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TYPE VIII PNEUMOCOCCUS: DEVELOPMENT OF SULFADIAZINE RESISTANCE, TRANSMISSION BY CROSS INFECTION, AND PERSISTENCE IN CARRIERS *

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THE purpose of the present study is to report the development of "sulfadiazine-tolerance" by a type VIII pneumococcus and the transmission of this strain to another patient by cross infection. The evidence to be presented in support of drug-fastness was obtained from the clinical course, laboratory findings, sputum examination, and growth studies of the pneumococci in media containing sulfonamides.

For the technic and detailed results of sputum examination, the reader is referred to previous publications. Serum therapy produced clumping and increased phagocytosis of pneumococci in the sputum, which was usually followed by a gradual decline in the number.[3] The characteristic response to chemotherapy, as seen in Wright stained smears of rusty sputum, was a sharp decrease in the number of organisms per field within 24 to 36 hours after treatment.[5, 6] Resistance to the drugs was suspected if the above effect did not occur or if the pneumococci returned to the sputum after an initial decrease, even though adequate blood sulfonamide concentrations were being maintained.[5, 6] The development of resistance was confirmed by in vitro studies of pure cultures carried out in the manner previously reported by one of the authors.[7]

RESULTS

The first patient (G. B.) was admitted to the hospital on September 6, 1941 with a right lower lobar pneumonia due to type VIII pneumococci.

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The clinical course, laboratory data, and sputum studies are presented graphically in figure 1. Before therapy was instituted, the sputum contained 85 pneumococci per oil immersion field,* the leukocyte count was only 3,400, but the blood culture was sterile. Within 36 hours after the institution of sulfadiazine therapy, there was a sharp decrease in the number of pneumococci in the sputum. After 50 hours of therapy, however, the pneumococci began to return to the sputum in increasing numbers despite high blood levels of sulfadiazine. This was interpreted as presumptive evidence that the organisms had become fast to the drug.[5, 6] Additional support for this concept was obtained clinically from the observations that the pneumonia had spread to involve the entire right lung and the blood cultures, which had previously been sterile, contained type VIII pneumococci. A total of 570,000 units of type specific horse serum was administered during the next 48 hours. Sulfathiazole was substituted for sulfadiazine in order to determine whether the pneumococci had retained sensitivity to this drug. The effect of serum was readily demonstrable by the agglutination and the increased phagocytosis of the pneumococci in the sputum. The rapid decrease in the number of pneumococci observed on September 13 was in part attributable to sulfathiazole since the organisms also showed the morphological changes characteristic of drug effect. The patient began to improve clinically and eventually made a complete recovery.

The second patient (M. G.) was first admitted on September 10, 1941 with a type III pneumonia involving the left lower lobe and made a prompt recovery following sulfathiazole therapy. During his stay in the hospital he occupied the bed adjacent to G. B. and additional close contact was possible since M. G. assisted the nurses and orderlies on the ward during his convalescence.† He was discharged on September 22 and returned a week later with a type VIII pneumonia involving the right lower lobe. The clinical course, laboratory data, and sputum studies are presented graphically in figure 2. Before sulfadiazine therapy was instituted the sputum contained only 2 pneumococci per oil immersion field‡; an adequate leukocytosis was present, and the blood culture was stertile. Examination of the sputum 48 hours later revealed that no therapeutic effect from the drug had occurred. In fact, the number of pneumococci had increased to 32 per field and the pneumonia had spread to involve the right middle and left lower lobes. The contact between G. B. and M. G. was then recalled. In view of the probability of cross infection and the failure to obtain a drug response either clinically or in the sputum, the pneumococci were considered resistant to sulfadiazine. A total of 390,000 units of type specific horse serum was administered within the next 24 hours and sulfathiazole was again substituted for sulfadiazine. The clumping and increased phagocytosis of the pneumococci in the sputum together with the marked decrease in number on October 7

* According to previous studies [4] this indicates a serious pneumonia.
† The pneumococci from G. B. were already sulfadiazine-fast (table 1).
‡ According to previous studies [4] this indicates a good prognosis.

TABLE I

In Vitro Susceptibility of Type VIII Pneumococci (Case G. B.)

Date	Chemotherapy	Culture Number	Source	Sulfadiazine mg. %				Sulfathiazole mg. %				Sulfapyridine mg. %				Control No Drug
				20	10	5	2.5	20	10	5	2.5	20	10	5	2.5	
9/6/41	None	1	Sputum	Cl	Cl	Cl	++++	Cl	Cl	Cl	Cl	Cl	Cl	+++	++++	++++
9/6/41	None	2	Sputum	Cl	Cl	++	++++	Cl	Cl	Cl	+	Cl	++	++++	++++	++++
9/10/41	Diazine	3	Blood	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++
9/10/41	Diazine	4	Blood	+++	++++	++++	++++	Cl	Cl	++	++	+++	++++	++++	++++	++++
9/10/41	Diazine	5	Sputum	+++	+++	+++	+++	Cl	+	++	+++	++	+++	+++	+++	+++
9/12/41	Thiazole	6	Blood	++++	++++	++++	++++	Cl	++	++++	++++	+++	++++	++++	++++	++++
9/12/41	Thiazole	7	Blood	++++	++++	++++	++++	+	++	++++	++++	++	++++	++++	++++	++++
10/19/41	None	8	Sputum*	+++	++++	++++	++++	+	+	+++	++++	++++	++++	++++	++++	++++
10/19/41	None	9	Sputum	++++	++++	++++	++++	+	+	++++	++++	++	++++	++++	++++	++++
10/19/41	None	10	Sputum	Cl	++++	++++	++++	Cl	Cl	Cl	++++	Cl	++++	++++	++++	++++
10/19/41	None	11	Sputum	Cl	+++	++++	++++	Cl	Cl	Cl	++	Cl	Cl	Cl	++++	++++
11/19/41	None	12	Sputum	†Cl	++++	++++	++++	Cl	Cl	+	++++	Cl	+	++++	++++	++++
11/19/41	None	13	Sputum	Cl	+++	+++	++++	Cl	+	++++	++++	Cl	+	++++	++++	++++
11/19/41	None	14	Sputum	+	++++	++++	++++	Cl	Cl	+	+	Cl	Cl	++++	++++	++++
11/19/41	None	15	Sputum	++	++++	++++	++++	Cl	Cl	Cl	+++	Cl	++++	++++	++++	++++
11/19/41	None	16	Sputum	++	++++	++++	++++	Cl	Cl	++	++++	Cl	++	++++	++++	++++
11/19/41	None	17	Sputum	+	++++	++++	++++	Cl	Cl	Cl	+++	Cl	Cl	++	+++	++++
11/19/41	None	18	Sputum	Cl	++++	++++	++++	Cl	Cl	++++	++++	++++	++++	++++	++++	++++
11/19/41	Type VIII Sensitive Control			Cl	Cl	Cl	++++	Cl	Cl	Cl	Cl	Cl	Cl	Cl	++++	++++

* Cultures 8 through 18 isolated by mouse passage of sputum.

† Sodium salts of drugs used.

Cl = Clear or no visible growth; +, ++, etc. = increasing degrees of turbidity.

was taken as evidence that both serum and drug had exerted the desired effect. The patient showed progressive improvement and subsequently recovered without complications.

Growth Inhibition Experiments. In addition to the clinical and sputum studies already discussed, 18 cultures of type VIII pneumococci were obtained from patient G. B. at intervals and tested for their ability to grow in media containing varying concentrations of sulfadiazine, sulfathiazole, and sulfapyridine. The results are recorded in table 1. It may be noted that the growth of two strains isolated before the institution of therapy was inhibited by sulfadiazine in a concentration of 5 mg. per cent and by sulfathiazole in a concentration of 2.5 mg. per cent. Cultures 3 through 7 were obtained during the sixth and eighth days of illness when the clinical diagnosis of resistance was made. At this time a striking change in the sensitivity of the pneumococci to chemotherapeutic agents had occurred. The growth of these five strains was not inhibited by concentrations of 10 to 20 mg. per cent of sulfadiazine and sulfapyridine, whereas the growth of four of the same cultures was definitely inhibited by similar concentrations of sulfathiazole. Therefore, the foregoing data substantiate the evidence obtained from the sputum that the pneumococci had become resistant to sulfadiazine, but still retained partial sensitivity to sulfathiazole. The data also lend support to the concept that sulfathiazole, as well as serum, contributed to the ultimate recovery of the patient.

Type VIII pneumococci were also isolated from the sputum of patient M. G. at the time when resistance to sulfadiazine was suspected. The results are recorded in table 2. Seven of nine strains obtained during hospitalization grew maximally in media containing 20 mg. per cent of sulfadiazine, whereas the other two strains were able to grow in 10 mg. per cent of the drug. On the other hand, the growth of seven of these same cultures was inhibited by concentrations of 5 mg. per cent or less of sulfathiazole. These data substantiate the evidence obtained from the sputum that sulfathiazole also played a part in the recovery of patient M. G. The fact that cultures from both patients were equally resistant to sulfadiazine and equally susceptible to sulfathiazole supports the concept that cross infection had occurred on the hospital ward.

A follow-up study of patients G. B. and M. G. revealed that both continued to carry mouse virulent, sulfadiazine-fast, type VIII pneumococci in their sputums for at least two months after the onset of their illness. All four strains isolated from G. B. one month after hospitalization (table 1) grew freely in 10 mg. per cent of sulfadiazine and two multiplied fully in 20 mg. per cent of the drug. One month later seven strains were obtained from G. B. and all multiplied in 10 mg. per cent of sulfadiazine, but were partially inhibited by 20 mg. per cent of the drug. Five cultures isolated from patient M. G. two months after hospitalization (table 2) grew freely in 10 mg. per cent of sulfadiazine and one of these was able to grow maxi-

TABLE II

In Vitro Susceptibility of Type VIII Pneumococci (Case M. G.)

Date	Chemotherapy	Culture Number	Source	Sulfadiazine mg. %				Sulfathiazole mg. %				Sulfapyridine mg. %				Control No drug
				20	10	5	2.5	20	10	5	2.5	20	10	5	2.5	
10/4/41	Diazine	1	Sputum	++++	++++	++++	++++	Cl	+	++	++++	+++	++++	++++	++++	++++
10/5/41	Thiazole	2	Sputum	++++	++++	++++	++++	Cl	+	++	++	++	+++	++++	++++	++++
10/5/41	Thiazole	3	Sputum	++++	++++	++++	++++	Cl	+	++	++	+++	++++	++++	++++	++++
10/5/41	Thiazole	4	Sputum	++++	++++	++++	++++	Cl	+	++	++++	+++	++++	++++	++++	++++
10/5/41	Thiazole	5	Sputum	++++	++++	++++	++++	+	++++	++++	++++	+++	++++	++++	++++	++++
10/19/41	None	6	Sputum*	Cl	++++	+++	+++	Cl	Cl	+	++	Cl	+	++++	+	++++
10/19/41	None	7	Sputum	+	+++	++++	++++	Cl	Cl	Cl	+	Cl	+	++++	++++	++++
10/19/41	None	8	Sputum	+++	+++	+++	+++	Cl	Cl	Cl	++	+	+++	+++	++	+++
10/19/41	None	9	Sputum	++++	++++	++++	++++	++++	++++	++++	++++	Cl	++++	++++	++++	++++
12/3/41	None	10	Sputum	†+	++++	++++	++++	Cl	Cl	++++	++++	Cl	Cl	+	++	++++
12/3/41	None	11	Sputum	++	++++	++++	++++	Cl	Cl	Cl	++++	Cl	++	++	++++	++++
12/3/41	None	12	Sputum	++	++++	++++	++++	Cl	++	++++	++++	++	++++	++++	++++	++++
12/3/41	None	13	Sputum	++++	++++	++++	++++	Cl	Cl	++++	++++	+	+	++	+++	++++
12/3/41	None	14	Sputum	++	++++	++++	++++	Cl	+++	++++	++++	++++	++++	++++	++++	++++
12/3/41	Type VIII Sensitive Control			Cl	Cl	++	++++	Cl	Cl	Cl	Cl	Cl	Cl	Cl	Cl	++++

* Cultures 6 through 14 were isolated by mouse passage of sputum.
† Sodium salts of drugs used.
Cl = clear or no visible growth; +, ++, etc. = increasing degrees of turbidity.

mally in 20 mg. per cent of the drug. It may also be noted that after two months (tables 1 and 2) the pneumococci were slightly more susceptible to sulfapyridine than to sulfadiazine, but that the growth of most cultures was best inhibited by sulfathiazole.

Discussion

The two cases presented in this communication are additional examples of the correlation previously reported [6] between the development of resistance as seen in the sputum and the ability of the pneumococci to grow in media containing increasing concentrations of the sulfonamide drugs.

The in vivo development of varying degrees of drug fastness has been reported by numerous investigators.[1, 5, 6, 7, 9, 10, 11, 12] Furthermore, the therapeutic efficiency of a particular sulfonamide appears to be closely related to its capacity to induce resistance. Thus, one of us found that in 17 per cent of cases given sulfanilamide the pneumococci returned to the sputum following an initial bacteriostatic effect despite adequate blood levels of the drug. A similar phenomenon was observed in 6 per cent of the cases treated with sulfapyridine and in only 2 per cent of those who received sulfathiazole.[5, 6] It was subsequently shown that these strains had acquired a considerable degree of tolerance to the sulfonamide drugs.[7] Direct confirmation of this observation was recently reported by Sesler and Schmidt, who demonstrated by in vitro experiments that "sulfanilamide resistance was developed most rapidly, sulfapyridine next in order, and sulfathiazole most slowly." [13] Carpenter and his co-workers have found that strains of gonococci "acquired only slight, if any, tolerance for sulfathiazole, although resistance to sulfanilamide was readily established." [2] Further study of sputum from patients with pneumonia has revealed that sulfadiazine occupies a position intermediate between sulfapyridine and sulfathiazole in that resistance develops in approximately 3 to 4 per cent of the cases. Although it is generally conceded that when organisms become fast to one sulfonamide they also acquire a comparable degree of tolerance to others, the results of the present study indicate that specific resistance to a particular drug may be induced. Similar observations have been made with *E. coli* [14] and with gonococci.[2] We believe, therefore, that the substitution of one drug for another may be of occasional value since both of our patients responded to sulfathiazole despite the fact that the pneumococci had become partially tolerant to sulfadiazine.

The prolonged retention of sulfonamide resistance by pneumococci has been emphasized by the studies of Schmidt, Sesler and Dettwiler, who found that completely resistant organisms maintained this property after more than 200 passages through normal mice.[12] Unpublished data of Hamburger, Sesler, Schmidt and Ruegsegger have revealed that sulfonamide-resistant pneumococci could be isolated from nose and throat cultures of carriers four months after recovery from the pneumonia.[12] Similarly the patients

G. B. and M. B. carried virulent, sulfadiazine-fast pneumococci in their sputums for at least two months after their discharge from the hospital. During that period they were potential sources of future cases of type VIII pneumonia which might have proved to be refractory to chemotherapy. If the frequency of drug-fast strains increases significantly in the general population by the indiscriminate use of sulfonamides, then it seems likely that the value of chemotherapy in pneumococcic pneumonia may be considerably reduced. During the past five years we have not noted any such tendency as judged by the examination of repeated specimens of rusty sputum from patients with pneumococcic pneumonia. Further investigation will be necessary in order to establish the duration of the carrier state and to devise methods of eradicating drug-tolerant pneumococci from the upper respiratory tract.

Summary

A case of pneumonia was reported due to a type VIII pneumococcus which was originally sensitive to sulfadiazine, but became resistant during the course of treatment. This same strain was then transmitted by contact to a second patient in an adjacent bed and later produced a pneumonia which also failed to respond to treatment with sulfadiazine. Drug-fastness was evidenced by the development of a positive blood culture during therapy in one patient, an extension of the pneumonia to other lobes in both patients, a marked increase in the number of pneumococci in the sputum in both patients, and the growth of these organisms in media containing 10 to 20 mg. per cent of sulfadiazine. On the other hand, the growth of these same cultures was inhibited by 5 to 10 mg. per cent of sulfathiazole.

After sulfadiazine-resistance had become apparent, serum and sulfathiazole were administered to both patients and recovery followed. Evidence was obtained from the sputum that each of the latter agents exerted its characteristic therapeutic effect. In addition, a follow-up study revealed that both patients continued to carry virulent sulfadiazine-resistant strains of type VIII pneumococci in their sputums for at least two months after hospitalization.

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A REVIEW OF THE DRASTIC SHOCK THERAPIES IN THE TREATMENT OF THE PSYCHOSES *

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DURING the past decade we have seen progressive changes in medical education and practice which have led to closer relationships between psychiatry and general medicine. We now accept psychiatry as that part of medicine which deals with the pathology and therapy of the person, instead of thinking of it as an isolated specialty dealing with advanced psychopathological disorders usually already admitted to institutions for treatment in the later stages of development when therapy is most difficult, more prolonged and less effective. Through this breakdown of the isolation of psychiatric medicine from basic general medicine we are now beginning to see the closest collaboration between the psychiatrist and internist in the study and understanding of the universal personal aspects of all medicine (shown in personality functions) and of the impersonal aspects shown in pathological expressions of disordered function of parts of the body (diseases of organs and systems). The effectiveness of present day clinical medicine, therefore, means an integration of these essential personal and impersonal components for examination and therapy of all types of illness.

In this lecture on the drastic shock therapies it is my obligation to present a résumé of their present results and status.[1]

The mode of action of these therapies is unknown, the clinical reactions are dramatic, the complications and contraindications are of great medical interest and import and should lead to a greater mutual dependence and collaboration between the psychiatrist and internist. The pharmacological shock therapies of insulin and metrazol as well as convulsive electro-shock therapy present numerous physiological, biochemical, psychological, electroencephalographic, electrocardiographic and neuropathological problems for research.

The use of these drastic therapies has been summarized recently by the United States Public Health Service in a survey of October, 1941. Questionnaires were sent to 356 hospitals and 85.7 per cent or 305 responded, of which 260 hospitals or 85.2 per cent were using shock therapies. An estimated total of 26,335 patients were receiving insulin shock therapy during the period of October, 1935 to October, 1941; 36,127 were receiving metrazol therapy and 7,771 patients were receiving electric shock therapy. The trend in the use of shock therapy in mental hospitals is summarized in table 1. The type of shock preferred is summarized in table 2.[2]

* Morning lecture before the American College of Physicians meeting, St. Paul, Minnesota, April 24, 1942.

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TABLE I
Trend in the Use of Shock Therapy in Mental Hospitals

Therapy Used	Hospitals Reporting Use of Specified Shock Therapy	Use of Shock Therapy Reported					Shock Therapy Being Replaced By				
		Increasing	Same	Decreasing	Discontinued	Not Stated	Insulin	Metrazol	Electric	Metrazol and Electric	Other
Insulin	219	23	59	50	75	12	—	23	27	18	4*
Per cent	100.	10.5	26.9	22.8	34.2	5.5					
Metrazol	228	32	47	67	74	8	4	—	88	—	1†
Per cent	100.	14.0	20.6	29.4	32.5	3.5					
Electric	129	84	24	5	1	15	—	2	—	—	1‡
Per cent	100.	65.1	18.6	3.9	0.8	11.6					

* Insulin-Metrazol (2); Metrazol and Curare; Typhoid.
† Insulin-Metrazol.
‡ Metrazol, Petrotoxin, Camphor.

TABLE II
Type of Shock Therapy Preferred *‡

Preferences Expressed by Hospitals Using	Number of Hospitals Reporting	Shock Therapy Preferred								Undecided and Not Stated	
		Insulin		Metrazol		Electric		Combinations			
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Insulin, Metrazol and Electric	111	14	2.6	9	8.1	66	59.5	8	7.2	14	12.6
Insulin and Metrazol	78	26	33.3	20	25.6	6	7.7	6	7.7	20	25.6
Metrazol only	30	—	—	11	36.7	6	20.0	3	10.0	10	33.3
Insulin only	21	8	38.1	—	—	2	9.5	—	—	11	52.4
Metrazol and Electric	9	—	—	1	†	6	†	—	—	2	†
Electric only	3	—	—	—	—	2	†	—	—	1	†
Miscellaneous	8	5	†	—	—	2	†	1	†	1	—
None	46	2	4.3	—	—	4	8.7	—	—	40	87.0
Total	306	55	18.0	41	13.4	94	30.7	18	5.9	98	32.0

* Replies to question "If only one form of shock therapy were available, which would you use?"
† Less than 10 cases in denominator.
‡ Reprinted by permission from the Am. Jr. Psychiat., 1942, xcix, 95.

In this lecture I should like to center my discussion around the three prevalent modes of shock therapy for the psychoses, i.e., insulin, metrazol, and electric shock convulsive therapy, with a brief résumé of the technics of administration, the indications and contraindications, reactions of the patients, complications of therapy and mechanisms of improvement. As is often true in the introduction of newer types of therapy, there is now evidence that the extreme enthusiasm of the early days has given way to careful appraisal of the assets and dangers of these types of therapy. These shock therapies have reaffirmed the psychosomatic view point of psychiatry and aroused a tremendous interest in research and speculation of all those who treat the mentally ill.

INSULIN SHOCK THERAPY

Insulin shock therapy was accidentally discovered by Manfred Sakel in 1933. Sakel attempted to use small doses of insulin in 1928 in an attempt

to relieve withdrawal symptoms of morphine addicts. When he produced deeper hypoglycemic reactions than planned he noticed marked alterations and improvement in the mental condition of his patients. Insulin shock therapy aroused tremendous interest on the continent and was first introduced in the United States by workers at Worcester State Hospital in 1936. At the American Psychiatric Association's 1937 meeting in Pittsburgh there was a symposium on hypoglycemia therapy and it was agreed at this time that the technic of treatment had been fairly well utilized and stabilized throughout the country. It was accepted that insulin therapy should be given only to psychotic patients of the schizophrenic reaction type. Preparation of the patient was reported as of the utmost importance and centered around an extremely thorough and meticulous physical examination including routine electrocardiographic studies, since it is well known that insulin may cause, even in small doses, disturbances of rhythm in cardiac deficiency. Likewise routine chest roentgenograms, complete blood chemistry, routine blood counts and urinalysis were carefully made in every case, but routine glucose tolerance tests were not given unless indicated by the blood chemistry and urinalysis studies. This special type of treatment was explained to the patient and his attitude and acceptance carefully evaluated. Contraindicative to insulin shock were essential hypertension, angina pectoris, coronary sclerosis or occlusion, valvular heart disease and myocarditis, hyperthyroidism, tuberculosis, and impaired renal, liver or pancreatic functions.

Technic of Treatment. It is the uniform organization in mental hospitals at the present time to have a special unit for insulin shock therapy consisting of a trained nursing staff and assistants. One nurse for each two to three patients is essential. It is likewise essential that a physician, familiar with this technic, must be present or immediately available at all times. Following the selection of the patient from both the physical and mental points of view regular insulin, and never protamine zinc insulin, is given to the fasting patient early each morning six times a week. The average total course of treatment is from two to three months. The initial dose is 15 units, which is increased daily by 5 to 10 units until signs of hypoglycemic coma begin to appear. The treatment is terminated for the average patient by urging him to drink a sugar solution three to four hours after the injection. The amount of sugar in grams used for termination is double the number of units of insulin administered. The solution should be warm to hasten absorption, and the glucose may be administered in water, weak tea or any fruit juice, but milk is not advisable. During phase one in insulin shock therapy the patient is usually able to drink, but if he should refuse to do so the solution must be given with a nasal tube or by the intravenous route. Thirty minutes later the patient is served breakfast and urged to eat. This constitutes phase one in the administration of insulin shock therapy.

Phase two is reached when the patient loses consciousness in the third hour. When this occurs the insulin dosage is kept stationary and termina-

tion is by means of the nasal tube or intravenous route. The experience of the physician and also close observation of the patient indicate that proper development of coma is characterized by loss of consciousness in the third hour and deep coma in the fourth or fifth hour. The shock dose varies tremendously in individual patients. Deep coma may be developed by as little as 20 units, whereas in other patients as many as 600 units fail to produce hypoglycemic symptoms. In our experience we rarely overstep 200 units since many untoward reactions are seen with a higher dosage, and experience shows that doses above 200 units rarely produce satisfactory and typical coma. Methods can be worked out in individual patients to sensitize them by zigzagging the dosage from day to day, cutting down on the caloric intake or the use of small doses of insulin the night before treatment. Our

TABLE III

Symptoms

Hours	Symptoms		Localization
First	Latent time Somnolence (97.2%) Hypotonia (97.4%)	Perspiration (99.1%) Salivation (90.1%)	Suppression of cortical and cerebellar activity
Second	Clouded consciousness Fine tremor Aphasia Apraxia Agnosia Fall of temperature Diminished exteroceptive sensitivity	Perceptual disturbances Motor excitement Confusion Psychotic syndromes	
Third	Loss of consciousness (100%) Primitive movements (71.5%) Forced graspings (71%) Clonic twitchings (79.2%) Myoclonoid twitchings Choreiform, Athetoid, Hemibalistic } movements (35.6%) Early torsion spasms	Motor restlessness Exophthalmos Dilated pupils Light reaction present Pulse rate increased Exteroceptive sensitivity increased	Release of the basal ganglia and hypothalamus
Fourth	Deepening stupor Increased tonus Coarse tremor Tonic spasms (82.6%) Tetanic postures Conjugate deviation of the eyes Late torsion spasms	Pupils small or large Pulse rate increasing or decreasing Signs of paralysis of the pyramidal functions Decreased exteroceptive sensitivity Increased interoceptive sensitivity	Release of the midbrain Suppression of pyramidal functions
Fifth	Tonic extensor spasms (34.1%) Posture reflexes Depression of tendon reflexes Deep coma Diminished sensitivity Lid and corneal reflexes sluggish Shallow respiration No corneal reflexes	Pin-point pupils No light reaction Pulse rate decreased	Release of the medulla oblongata

experience was similar to that of other observers in that we find direct correlation between the patient's acceptance of treatment and the dosage needed to produce coma. Frostig [3] has given us a table of symptoms correlated with each hour in accordance following table 3. These are of help and value in the selection of time of termination.

Time and Technic of Termination. There should be no definite rule for the time of awakening such as 10:30 or 11 a.m. Each patient has to be carefully followed through his coma and awakened at the most opportune time. It is a safe rule never to leave the patient in a deep coma more than 45 minutes, nor should any patient be allowed to continue more than 30 minutes with absent corneal reflexes. Careful charts should be kept with a notation in red when the patient becomes comatose as well as a regular testing of the corneal reflexes. Sakel emphasized the termination of treatment in relation to the patient's mental reaction type. For instance, the patient in a catatonic stupor is brought out of the hypoglycemia at the point where he shows the most mental activity; paranoid patients with systemized delusions are allowed to go into deep coma and in patients with catatonic excitement hypoglycemia is terminated when they grow somnolent.

You cannot estimate the depth of coma by reflex changes of the upper neuron type. A positive Babinski sign may appear in a very light coma in some patients and not appear in others until a very deep coma and a medullary phase have developed. In deep coma there may be a hypotonia and areflexia, or the patient may be tense, excited with myoclonic movements that make testing of the reflexes impractical. The stage of insulin coma can be carefully evaluated by eye movements as follows [4]:

1. Nystagmus on attempted fixation. Here also may be seen such things as lid retraction, myoclonic, conjugate deviation, a positive Babinski sign, etc. Patient is usually able to talk a bit and perhaps swallow.
2. Spontaneous pendular nystagmus or conjugate deviation which do not disappear upon stimulation. Here corneal reflexes remain active. Patient is unable to fix.
3. Nystagmus upon stimulation only. Here spontaneous eye movements have ceased and eyes remain at rest near midposition. If the head is rolled quickly a short period of pendular nystagmus will follow.
4. No nystagmus on stimulation. Here is a contracted fixed pupil, and decreased or absent corneal reflexes. Tendon jerks may be normal or decreased.
5. Paralytic respiratory coma. An intercostal paralysis with respiratory depression. Patient shows gasping with shallow, irregular respiration and dilating pupils.

We have here phenomena similar to that occurring in anesthesia. It is important that the physician remain with the patient during phase two. It

is obvious that no patient should be allowed to reach stage five. The above stages correspond closely to the accepted phases such as mild hypoglycemia, the precomatose state, the onset of coma, the deep coma, and the stage of tetanoid seizure or respiratory paralysis. The usual termination of coma is by means of the nasal tube route. The technic here must be a careful one in ascertaining the position of the tube before the sugar solution is administered. This is best done by aspirating some of the gastric contents by means of the suction bulb and testing it on litmus paper. If no fluid can be aspirated, by introducing air through a syringe one can listen with the stethoscope over the stomach. The intravenous injection of glucose should be used for termination in all emergency situations. Some clinics use the intravenous termination routinely but since this tends to thrombose veins and since the sudden awakening produced by injection has less favorable effect than the gradual one resulting from gavage we favor this route of administration. The patient must always be given carbohydrate by mouth after awakening and must always be given a substantial meal. In case the patient routinely arouses slowly, additional intravenous injections should be given. Usually the patient on awakening has a short period when he is free from his troublesome preoccupations. It is our policy to employ psychotherapy at this time.

The complications of insulin therapy are usually reviewed under four main headings. The first centers around the central nervous system disorders such as aphasia and hemiparesis, which are usually transitory, although they may persist for two to three days. It is our policy to terminate insulin shock when such complications occur. Epileptiform seizures often occur during the first two hours of treatment. If the patient remains in good condition following the convulsion the treatment need not be terminated. It has been noted and emphasized by many that following epileptiform seizures clinical improvement follows. Status epilepticus is rare. The late tetanoid convulsions occurring after the third hour represent acute danger signals indicating the abrupt termination by the intravenous route. Cardiovascular disturbances represent an important complication. An irregular pulse is common and of little significance during the first hour of treatment, whereas a rapid, thready pulse in late hours of treatment indicates cardiac fatigue. Auricular fibrillation may occur. Cardiac failure is rare but does occur, as does general circulatory collapse. Immediate termination by the intravenous route is indicated in the above complications. Among respiratory disturbances the most common complication is aspiration, since many patients have a marked overproduction of saliva associated with the loss of the swallowing and cough reflex. The head of the bed should be raised so that the patient is sitting upright and his head allowed to hang, thereby letting him drool. Sheet restraints are employed to help the patient maintain this position. Laryngospasm may develop as part of the general tonic muscle spasm and this, of course, calls for immediate termination. Central respiratory failure may set in without warning and

necessitates prompt termination by intravenous glucose. Injections of lobeline and the use of oxygen are the treatment of choice here. Pulmonary edema likewise has been reported. Intravenous glucose slowly injected will usually care for this condition. The use of adrenalin is contraindicated. The fourth and miscellaneous set of complications center around the allergic reactions manifested by local irritation at the site of injection of insulin. So-called insulin lipomata may develop with resulting atrophy of the subcutaneous tissues and muscles. Adrenalin and intravenous calcium are used in the treatment of this complication. The most serious and, fortunately, infrequent complication is delayed awakening or prolonged coma. If the patient does not awaken after tube feeding or becomes unconscious after swallowing, intravenous glucose should be given not later than 30 minutes after the original sugar intake. If the patient does not arouse, an immediate blood sugar determination should be made to show the presence or absence of hypoglycemia. At times the patient may show a high blood sugar and yet remain comatose, cyanotic, dyspneic and may be having convulsions. If the blood sugar level is normal or above normal, it is obvious that no additional sugar should be given. The patient should be kept quiet and warm and stimulants withheld unless actually needed to preserve life. Oxygen inhalations are sometimes of benefit. Intravenous injections of Betalin have been advocated. Convulsions are usually controlled by two grams of potassium chloride. Blood transfusions have been used with some success. Death during insulin shock therapy is usually due to this complication and our experience indicates the most important precautions to avoid excessive doses of insulin, terminate the treatment at the proper time, and avoid prolonged periods of deep coma, never allowing a duration of more than 45 minutes and less in many cases.

Changes During Treatments. Numerous papers have been written concerning the physiological changes during treatment including the well known increase in weight, changes in brain metabolism, decrease in blood sugar levels to about 25 mg. per cent during hypoglycemia, and the development of mild leukocytosis without changes in the red blood cell count and hemoglobin during hypoglycemia. The serum lipoids, other than cholesterol, are raised during treatment, and this fact is of great interest since it has long been known that in schizophrenic reactions the serum lipoids are low and in cases that recover the rise is especially noticeable.

At the present time there is no clear cut evidence of actual brain damage, although animal experiments tend to show that prolonged coma produces irreversible histopathological changes. In all clinics it is accepted that the depth of coma determines in all cases whether the pathological changes are reversible or whether definite nerve cell destruction may occur.

Mental Changes and Possible Mechanisms of Improvement. Fairly characteristic changes are noted in patients who improve under insulin therapy. During the precomatose stage the patients show interesting emotional changes which may vary from coöperation and contentment to an-

tagonism and rage with all stages of gradation between the states of calmness and excitement. The patient's prevalent mood disturbance swings to the opposite extreme. The previously tense patient may become placid, and the hyperkinetic, restless patient will become quiet. Often during the precomatose stage the patient discusses his conflict material and troublesome preoccupations. Patients who have been questioned regarding their experiences during the coma will usually be nonproductive and many of them state they are experiencing death. It is to be reëmphasized here that patients who accept the treatment will be less disturbed during both precomatose and comatose phases. When the treatment has been terminated many patients are frequently coöperative and show a marked change in attitude from withdrawal, suspicion and absorption in their conflict material to acceptance of treatment and interest. This may last for a few minutes or for more prolonged periods especially in the patients who later show improvement. Adjustment to the group including both relationships to other patients and to the professional and non-professional personnel of the hospital are important. The factor of the mechanism of improvement, in my opinion, is not on the basis of biochemical changes as much as it is a psychotherapeutic one. The interest of the entire staff, and the prolonged individual attention in the care the patient receives from the medical staff and nurses during and between the shocks are of paramount importance. These psychotherapeutic adjuncts are clearcut and less theoretical than the stress placed in the literature on anoxemia. The reduced consumption of glucose and oxygen by the brain is not the only metabolic disorder that takes place during insulin hypoglycemic shock. Katzenelbogen [5] postulates that the mode of action is that usually attributed to non-specific protein therapy namely, activation of the functions of organs (protoplasma activation), or the changes which take place in the constitution of the body fluids, or both. This may well be applied also to non-specific shock therapy.

Results of Treatment. The literature shows a marked discrepancy in the results of treatment, varying from 70 per cent complete recovery to 20 per cent improvement, with even poorer results in untreated cases. There is no doubt that this is due to lack of uniformity in the application of insulin shock as well as in the diagnosis of schizophrenic reactions. Likewise, the literature of spontaneous remissions varies from 10 to 40 per cent according to the center from which one obtains results. The results reported by Ross and Malzberg [6] from New York State are about the average from the world over. There were 1757 patients treated with insulin and the results were: recovered, 11.1 per cent; much improved, 26.5 per cent; improved, 26 per cent; unimproved, 26.2 per cent; died, 1.1 per cent. The number of recovered cases, as well as the total number showing improvement, was about three times that in a control group receiving the usual institutional treatment. Reports of a one and two year follow-up [7] indicate that the percentage of patients described as recovered remained almost constant, but that there has been a reduction in the percentage of cases showing a lesser

degree of improvement. The total percentage of recoveries and improvements had fallen from 63.5 per cent to 48.2 per cent, one year later. The latter percentage, however, was still most favorable when compared with the results from other types of therapy. Cases in which psychotic manifestations were of short duration had the best possibilities of recovery.

Prognostic factors have been carefully evaluated by Cheney and Clow [8] who state that the following are the most important ones since they appear to be indicative of favorable results.

1. Acute onset in contrast to gradual change in personality or attitude.
2. Onset with a precipitating factor (such as an obvious conflict or loss of love object).
3. The productivity in psychotic symptoms and flexibility, especially in paranoid ideas, in contrast to a rigid paranoid system.
4. Preserved affectivity.
5. A prepsychotic personality with capacities for interpersonal relationships and sublimation.
6. Marked depressive and neurotic features.

Preservation of normal emotional reactions previously emphasized appears to be one of the most important things along with an acute onset. Previous attacks with remission apparently do not have any effect on the general outcome with insulin shock treatment. In our clinic [9] and others [10] attempts have been made to use special psychological tests, especially the Rorschach test, to obtain prognostic hints regarding the response to this type of therapy. The greatest care must be taken to limit patients receiving insulin shock therapy to clearcut psychosis of schizophrenic type, since it is generally accepted that other psychotic reaction types either do not respond to insulin or respond better to the other methods of treatment.

Metrazol and Electric Convulsive Shock Therapy

The development of convulsive therapy in general paralleled that of insulin shock therapy. Ladislau von Meduna, in 1933, began using camphor intravenously to produce convulsions and reported encouraging results. Later he developed the use of metrazol, a synthetic product, soluble in water and rapidly absorbed, which could be given intravenously in 10 per cent solution and which within five to 15 seconds produced a convulsion. The same careful method of preparation for this treatment as that described for insulin is carried out, including roentgenograms of the spine to rule out old injuries or structural deformities. The patient is best left without sedation for 12 hours prior to injection and the treatment is given on a fasting stomach. All false dentures should be removed and the practice should be to hyperextend the patient's dorsal spine, since in this position the risk of vertebral fracture is reduced. The initial dose, from 3 to 5 c.c. of the drug, is given intravenously and rapidly. If no convulsion takes place in one

minute the injection is repeated with one half to one c.c. more than the amount originally given. Experiments indicate that the fatal dose is about 30 c.c., but in our experience we have never given more than 12 c.c. in one injection. The convulsion is severe and usually starts with a wide opening of the mouth at which time a flexible gag is inserted. There is usually a cough or cry, a gradual increase in general tonus, and then there appear clonic movements which rapidly increase in intensity. These clonic movements are then followed by a tonic phase which may be prolonged, producing

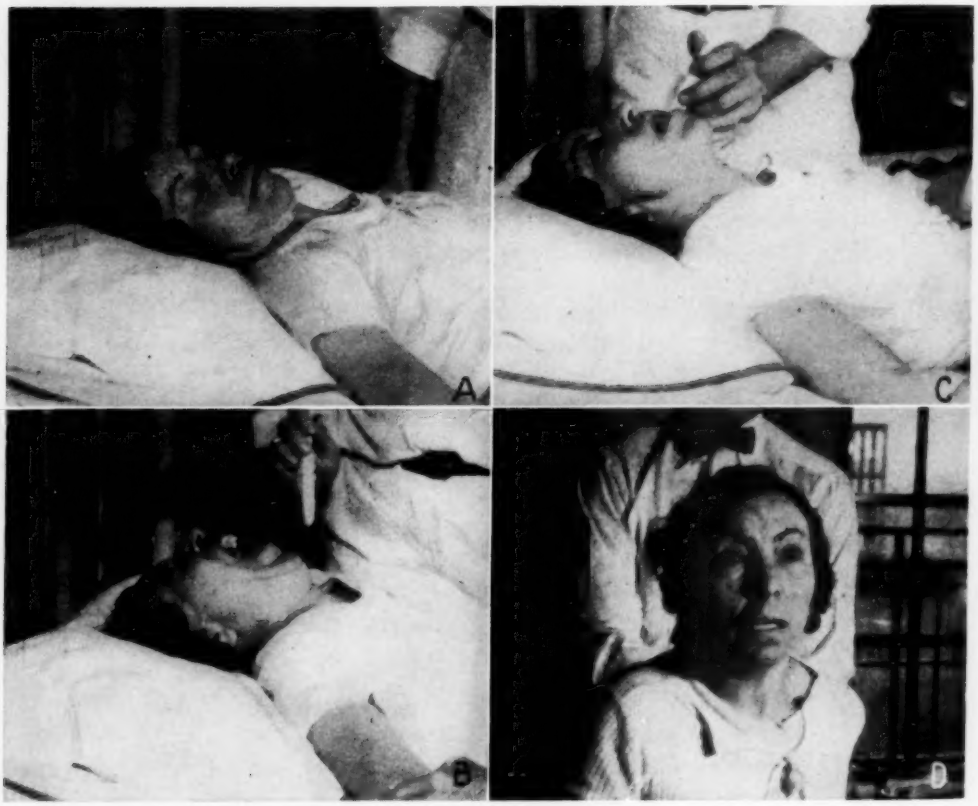

FIG. 1. *A*. Following injection of Metrazol and prior to convulsion. *B*. Beginning of seizure. *C*. End of seizure. *D*. Post-convulsive excitement.

extreme rigidity. A second clonic phase, which gradually decreases in intensity, ends the seizure. This sequence, although like an epileptic fit, differs from it in that the epileptic convulsion does not have the initial clonic phase. At the beginning of the seizure the pupils dilate and become fixed. During the convulsion urination and ejaculation frequently occur. Pyramidal tract signs such as ankle clonus and unilateral or bilateral Babinski signs appear. The paroxysm ends with a period of apnea which lasts several seconds, during which the patient becomes cyanotic and livid and the eye-

balls turn upwards. A deep inspiration terminates this period of apnea which is followed by snoring-like respirations. Following the convulsion the patient is frequently excited, shows marked anxiety and confusion, and on occasions nausea with vomiting may develop. Care should be exercised to prevent aspiration.

Frequency of Treatment. It was our usual policy to give metrazol treatments twice a week and it has been our routine to limit such treatments to a total of 8, although in many clinics as many as 25 convulsions are in-

FIG. 2. *A.* Before treatment showing apprehension, confusion and bewilderment. *B.* Beginning of coma. *C.* Deep wet shock. *D.* Positive Gordon.

duced. We usually find that patients who improve, especially the affective depressive reactions, begin to improve following the third or fourth seizure.

Indications and Contraindications. Although metrazol convulsive therapy was originally proposed by Meduna for schizophrenic reaction types the experience of most clinics indicates the main field of effectiveness is in the affective disorders. It has not, however, been entirely abandoned in schizophrenia. In the study of our 400 cases improvement occurred in schizophrenia and it is still utilized in the catatonic reactions.

The results in the depressive psychoses are frequently striking. Metrazol should not be used indiscriminately in these reactions, but in the deep-seated, prolonged depressive states and in those patients who become exhausted from agitation and who make repeated suicidal attempts it is clearly indicated. This group includes the agitated depression, and various types of involutional depressive disorders. The results in the manic reactions are not as outstanding as in the depressive group. We doubt very much the advisability of the use of metrazol therapy in severe psychoneurotic reactions. The contraindications are practically the same as for insulin therapy, namely, the presence of cardiovascular disease, abnormalities of the blood or urinary constituents, febrile conditions, thrombophlebitis, tuberculosis, cachexia, bone diseases, and the presence or history of a skull or back fracture. The most serious complications consist of dislocations and fractures which result from the extreme violence of muscular contractions during the seizure. Dislocation of the jaw may occur, although reduction is simple and easily carried out after the seizure while the patient is still unconscious. Dislocation of the shoulder is less frequent and can be prevented by keeping the arms in adduction close to the trunk, the forearms crossed on the chest. Rarely there are fractures of the humerus and even of the femur, but the most important and unfortunately the most frequent appear to be the fractures of the thoracic vertebrae. The original paper pointing out these fractures by Polatin, Freidman, Harris and Horwitz, of the New York State Psychiatric Institute, reported fractures occurring in as high as 49 per cent of the patients. In our series careful roentgenological studies were made of all cases, showing the incidence of fractures to be less than 7 per cent. Fractures usually occur in the mid-thoracic area and are of a compressed type. The absence of subjective complaints from these patients, even with one or more vertebral bodies compressed, is striking, and there appears to be no relationship between the intensity of the complaint of backache and the degree of bone injury. If such fractures occur the orthopedic consultant puts the patient in a cast or corset brace for several weeks, during which time the patient is ambulatory. The sequela is usually a slight gibbus. Naturally there has been considerable work done to prevent fractures. The most striking, as well as the most important advance in the prevention of fractures, has been the introduction of curare by Bennett.[11] This drug is now in widespread use in most psychiatric clinics. It is given intravenously, relaxing the peripheral muscles through its selective, depressive action on motor nerve endings. One c.c. of the aqueous solution of curare represents 10 mg. of the crude drug. The dosage is usually 1 c.c. per 20 pounds of body weight, and it is administered intravenously over a period of one to one and one-half minutes. Following the intravenous injection of curare, metrazol is given in two to three minutes. Typical clonic-tonic-clonic sequence is present, but the degree of rigidity is markedly reduced and the

violent clonic spasm is absent or greatly reduced. The extremities of the patient who has been curarized can be passively moved at will during the convulsion. It is wise to give prostigmine following the use of curare and we find that many patients vary in their sensitivity to this drug. The other complications frequently observed represent memory impairment similar to that seen in the organic reaction types. The patients, as a rule, both before and following individual treatments, are extremely apprehensive and frequently speak of dying, and many show an accentuation of the pathoplastic features of their illness. Dr. Neubuerger and I [12] have summarized the results of animal experimentation which on the whole indicate that brain changes are present but are for the most part reversible. Apparently some degree of cortical damage does occur as shown in the cellular changes. These changes appear to be secondary to vascular changes.

Results of treatment can be tersely stated. The general agreement is that the use of metrazol convulsive therapy in the affective reaction is almost uniformly favorable and that rapid improvement occurs in a large majority of these cases. The results in the schizophrenic reactions do not substantiate the early claims of the proponents of this type of therapy and insulin shock treatment continues to be the method of choice in schizophrenic reactions.

Electric Convulsive Therapy

Since 1937 electric convulsive therapy has gained considerable prominence in the treatment of psychotic reactions. Although it has been known for many years that electricity produced convulsions, it was not until Cerletti and Bini [13] inaugurated this type of therapy in Italy that it gained prominence. It was soon adopted throughout the continent and was introduced in this country at the New York State Psychiatric Institute early in 1939. There are two methods in use at the present time, one of which employs an alternating current and produced unconsciousness in the patient, and the other, developed by Berkwitz, uses faradic shock which is not associated with loss of consciousness. This latter method, although most interesting and well developed by Berkwitz, thus far has not been given universal acceptance. Electric shock is purely an empirical form of therapy. Several types of machines have been developed to supply the alternating current which produces convulsions by means of the application of a known potential difference between the fronto-temporal regions for a known period of time. A neat set of adjustable electrodes is applied to the frontal temporal area and a 60 cycle alternating low frequency current is used through a special timing device, allowing the current to flow 0.1 or 0.15 of a second as desired. A scale records in ohms the resistance which is found between the two terminals placed on the patient's temporal regions. One dial indicates the milliamperes, and another dial allows the desired voltage to be set. The electrodes are attached to insulated clips for ease in handling, and the terminals themselves

consist of a ball of moderately fine copper wire. The terminals are covered with a cloth sack soaked in 20 per cent saline solution. Electrode jelly, containing 20 per cent sodium chloride, is spread over the temporal contact areas. The amount of current varies from patient to patient. For the first treatment we usually set the timer at 1/10 of a second and the voltage at 80. The milliamperage delivered is usually between 400 and 1000. As a rule the voltage has to be raised gradually as treatment progresses and frequently a

FIG. 3. *A*. Restlessness during coma. *B*. Convulsion during coma. *C*. Excitement following gastric gavage. *D*. Recovery.

voltage of 120 may be required. The accompanying pictures show the sequence of events in electric convulsive therapy.

Following the passage of the current the patient may have a minor or major grand mal seizure, complete abortion of the convulsion, or a petit mal seizure. Consciousness may be lost immediately but only for a few minutes. There is an initial generalized, myotonic flexion of the body, and if not restrained the patient may assume a sitting posture momentarily. There may be only a loss of consciousness and flushing of the face with accelerated pulse

rate and shallowness of respiration. The characteristic retrograde amnesia for the seizure occurs. Petit mal responses are usually due to insufficient voltage. Some clinicians attempt to limit the application of this therapy to the minor seizure and no final conclusions are yet available as to the results of such treatment. The grand mal seizure is typically an epileptic one. Consciousness is lost immediately after the shock button is pressed and the convulsion occurs instantly or after a lapse of 30 to 60 seconds. There may be a cry. The patient will usually open his mouth and at this time a flexible

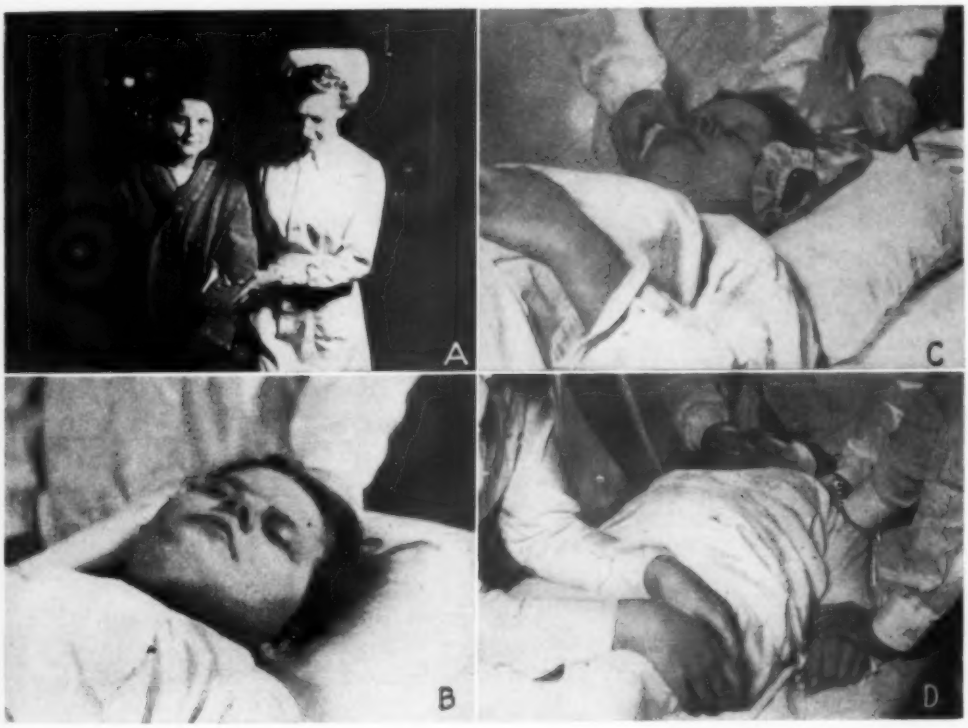

FIG. 4. *A*. Lack of apprehension prior to electric shock treatment. *B*. Muscular relaxation following Curare. C. Application of electrodes. *D*. Support given during electric shock convulsion.

gag should be inserted. The tonic generalized contraction is associated with flushing of the face and lasts about 10 seconds, followed by the clonic phase which may be associated with involuntary loss of sphincter control, marked cyanosis of the face, and frothing at the mouth. During the seizure the eyeballs are turned upwards resembling a conjugate deviation, the pupils are dilated, the cyanosis appears to be more marked and lasts longer than with the metrazol convulsion. At the end of the fit the deep and superficial reflexes are usually absent but within a minute or two the tendon jerks are brisk with

ankle clonus, positive Babinski and Hoffman's signs. The seizure lasts from 30 to 45 seconds, following which the patient is gradually restored to consciousness and within a few minutes is able to talk drowsily although he is amnesic and confused.

Electric convulsive therapy appears to have the following advantages:

1. Immediate loss of consciousness associated with the painless electric shock and the complete amnesia for the whole treatment remove many of the subjectively disagreeable elements in the pharmacologically produced convulsion.
2. Lack of discomfort following the treatment aids in securing the needed coöperation of the patient.
3. It removes the inconvenience of frequent intravenous injections.
4. It is possible to produce both a grand mal and petit mal convulsion.

The main indications for the use of electric convulsive therapy are in the treatment of the affective reaction types. It is our policy to induce eight convulsions, two each week. There is the same tendency as seen in metrazol convulsions for improvement to be noted following the fourth or fifth seizure. Our experimental work (Whitehead, Neubuerger, Rutledge and Ebaugh [14]) indicates that clearcut brain changes do occur which for the most part are reversible. Brain waves show the development of characteristic dysrhythmia, which in successfully treated cases gradually disappears, however, after the termination of the treatment. Curare is given intravenously in the electric shock convulsive treatments and at the present time the following routine for the prevention of fractures both in metrazol and electric shock convulsive therapy is utilized by most clinics.

1. The intravenous injection of curare—1 c.c. equal to 10 mg. of the drug.
2. The use of a hard mattress beneath which is a hard surface. A blanket roll is placed so that it will hyperextend the dorsal spine. So-called re- in hyperextension.
3. The shoulders and hips are held firmly by nurses and attendants.
4. The removal of false dentures if present, and of hairpins in electric convulsive therapy.
5. The use of a mouth gag of resilient type.
6. A suitable number of assistants.

I have attempted to discuss thus far the prevalent use of the drastic therapies, insulin shock, metrazol and electric convulsive therapy in the psychoses. I hope I have emphasized the serious possibilities in the employment of these types of therapy. Deaths occur in each type of therapy as shown in table 4, obtained from the United States Public Health Service Shock Therapy Survey.[15]

TABLE IV

Deaths Reported for Mental Hospital Patients Receiving Shock Therapy

Type of Control	Insulin				Metrazol				Electric			
	Hospitals Reporting*	Number of Cases Treated	Deaths		Hospitals Reporting*	Number of Cases Treated	Deaths		Hospitals Reporting*	Number of Cases Treated	Deaths	
			Number	Per Cent			Number	Per Cent			Number	Per Cent
State Hospitals	122	2,457	121	4.9	132	28,655	47	0.2	67	5,495	3	0.05
Federal Hospitals	23	912	7	0.8	12	341	2	0.6	1	26	—	—
City and County Hospitals	7	982	8	0.8	12	1,464	—	—	8	—	—	—
Private Hospitals	46	2,607	8	0.3	46	4,221	2	0.04	29	1,186	1	0.08
Psychiatric Wards in Selected General Hospitals	6	631	3	0.5	8	492	1	0.2	8	500	—	—
Total	204	7,589	147	0.6	210	35,173	52	0.1	113	7,207	4	0.05

* Includes only hospitals reporting number of cases treated and number of deaths.

SUMMARY AND CONCLUSIONS

I have presented the present day methods and therapeutic application of the drastic therapies of the psychoses by the use of pharmacological shock therapy, such as insulin and metrazol and electric convulsive therapy. The mode of action of these therapies continues unknown although there have been many theories regarding their beneficial therapeutic effect. These therapies undoubtedly serve as an ace in the hole to supplement other therapeutic methods. Insulin shock therapy may make schizophrenic patients more accessible to psychotherapy. Metrazol is now being discarded by many clinics for electric convulsive therapy which is simpler and perhaps less drastic and hard on the patient, and because, when combined with curare, the complication of fractures is eliminated. Both metrazol and electric convulsive therapy have proved to be of little benefit in the treatment of schizophrenic reactions but of considerable benefit in the treatment of the affective disorders, especially the depressive reactions. These drastic therapies were inaugurated with uncontrolled enthusiasm and, as has been true historically in other new types of therapy, have probably been made to appear more promising than is actually the case. On the other hand they have aroused tremendous interest in mental hospitals and have emphasized the importance of treatment of serious psychotic reactions, with the resultant changes in the attitude of the personnel of these institutions as well as patients and their relatives and the general public. They have presented numerous problems for research of physiological, psychological, biochemical and histopathological import and have increased further the necessary collaboration between internal medicine and psychiatry.

Whether these procedures are a permanent part of our therapeutic armamentarium or not cannot be stated at this time. Better controls, greater

uniformity, a better balanced psychotherapy with shock therapy, and better follow-up studies based on complete social, physical and psychological examinations must be made.

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TUNING FORK AUSCULTATION: A TEST FOR ABDOMINAL ADHESIONS *

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It is not often that anyone wishes to open the grave and exhume the corpse to ascertain why he died an untimely death. But this is the circumstance which now confronts me. In 1922, I published [1] a description of a new diagnostic technic. That paper attracted scant attention, for reasons now clear to me. Therefore, except for R. T. Ellison, who was then working in my clinic, this test lacked further study and confirmation.

The test is a combination of auscultation and vibratory percussion, and serves as a bedside addition to physical diagnosis. Its purpose is to determine, by means of a tuning fork and a stethoscope simultaneously applied to the abdomen, the likelihood of adhesions in the upper right quadrant.

Its scope is limited. It will detect adhesions involving only the stomach, duodenum, portions of the colon and the gall-bladder and liver. It will not detect adhesions between the omentum and the biliary organs, nor will it detect appendiceal, pelvic or other abdominal adhesions so far as I am now aware.

Even though thus limited to the detection of certain types of upper right quadrant adhesions, acquisition of such information is very important for the patient's welfare because it will facilitate an earlier decision as to the necessity for operation. This quick and inexpensive test will, with experience, obtain this information in a surprisingly high percentage of cases.

In 1924, Ellison [2] undertook a review of 50 unselected cases in which he tabulated a comparison of the evidence of upper right quadrant adhesions as obtained by roentgen-ray with similar evidence as determined by "tuning fork auscultation." He expressed the opinion that a positive tuning fork test is strong presumptive evidence of upper right quadrant adhesions because he found it in agreement with roentgen-ray findings in 89 per cent of his cases. He considered a negative test less accurate because it agreed with roentgen-ray evidence in only 58 per cent. Ellison inferred, therefore, that roentgen-ray evidence of adhesions was more accurate than "tuning fork auscultation." None of his cases reached the operating table for final confirmation as to which technic was the more reliable.

During this long interval I have become more and more convinced of the accuracy of this simple test, as I have learned by experience to interpret it more correctly. I have, however, discarded the attempt to make the finer diagnostic distinctions as to location and degree of adhesion formation as presented in my original article. I have learned that it is wiser either to exclude all "doubtful positive" tuning fork responses or else include them in the negative group. A clean cut and consistently positive response will

* Received for publication March 25, 1942.

usually mean upper right quadrant adhesions as revealed by operation irrespective of the roentgen-ray evidence to the contrary (see tables 3 and 4).* Likewise, a clean cut and consistently negative response will exclude adhesions. Fine congenital adhesions, as a rule, will not give a positive response unless some degree of inflammatory adhesion formation between gall tract and stomach, duodenum or colon co-exists.

Verbrycke [3] in 1940 advanced the value of combining a cholecystogram and a barium enema roentgenographic examination in determining adhesions between the hepatic flexure of the colon and the gall-bladder. A perusal of the literature from 1924 fails to reveal any further publication on this subject. So the tuning fork test died an untimely death for lack of interest and has remained buried for nearly two decades. I now propose to open the grave and reëxamine the corpse in the hope that it may be found merely in a state of suspended animation and with the further hope that by presenting the following study this excellent test may be revived and may serve a larger field of usefulness.

Criteria Determined and Material Studied. In preparing this article only the author's office files (1926–1939) have been consulted, and with but one objective: to present unselected cases in which the tuning fork evidence is compared with the roentgen-ray evidence of upper right quadrant adhesions and then to evaluate the accuracy of each test by the actual findings at operation.

Approximately 500 case records were examined. More than four out of five were discarded for these reasons:

First, the patient was operated upon elsewhere and the operative findings were not reported to the author by the surgeon. For this reason it was necessary to exclude more than 200 cases from this statistical report.

Second, the patient had had a tuning fork appraisal but did not have a cholecystographic or progress meal roentgen-ray study. There were found to be approximately 150 such cases. Analyzing them the author found two reasons for this omission: either the patient economically was unable to undertake the expense of roentgen-ray study, or the clinical evidence including tuning fork auscultation was so clearly indicative of upper right quadrant pathologic lesions that operation was performed on this evidence alone.

Third, the patient had had either a cholecystogram, a progress meal study, or both, but the author found to his humiliation that he had not recorded (or had failed to make) a tuning fork appraisal. There were approximately 50 such cases.

Results of Material Studied. Having to exclude so many cases for the foregoing reasons there remain 85 cases in which all criteria were fulfilled

* Feldman has recently stated "The roentgen determination of adhesions in the upper right quadrant involving the gall-bladder has always been of doubtful value." Ref. FELDMAN, MAURICE: A clinical roentgenological review of the literature of 1940, pertaining to the digestive tract, Am. Jr. Digest. Dis., 1941, viii, 279.

TABLE I

42 Cases in Which Both Tuning Fork Test and Roentgenological Findings Agree and Are Correct as Proved by Operation

Case	Sex Age	T.F. Response	Roentgen-ray Evidence for U.R.Q. Adhesions	Operating Table Findings and Remarks
2. M.L.	F 30	*1, 2	Non-visualized gall-bladder; 1 large negative shadow. Duodenal cap failed to fill and is irregular in outline. Adhesions (?)	Biloculated g.b.; 1 large cholesterin stone in fundal pocket. Dense adhesions between duod. and both g.b. and liver. Cholecystectomy.
4. L.L.	M 60	*1, 2, 3, 4	Poor visualization; positive stone shadows; irregular, nonretentive duod. Suggestive for duodenal and colon adhesions.	Dense adhesions between g.b., liver, duodenum, hepatic flexure and trans. colon; 2 stones in g.b. Cholecystectomy with difficulty. Adynamic ileus. Recovery.
9. G.B.	M 56	1	Pathologic gall-bladder and possible stones. Fairly well preserved function; U.R.Q. adhesions (?)	Large, tense, thick-walled g.b.; many stones; adhesions between g.b. and duodenum. Cholecystectomy.
12. A.I.	F 34	1, 2	G.B. has been previously removed. Progress meal suggests U.R.Q. adhesions.	Dense adhesions between duodenum and liver. Release of adhesions.
20. E.E.	F 37	1	Cholecystitis. Adhesions to duodenum. No stone shadows. † (Note: Biliary drainage microscopy is positive for stones.)	Normal appearing gall-bladder adherent to duodenum and containing 1 large stone. Cholecystectomy.
31. D.F.	F 23	Negative	Normal cholecystogram. Normal progress meal.	Normal g.b.; no stones; no adhesions. Appendectomy.
39. M.B.	F 31	Negative	G.B. functions to cholecystogram. 1 stone shadow. No evidence of adhesions. Clinical diagnosis: g.b. typhoid carrier.	Small, non-adherent g.b., containing 1 stone. Hepatitis. Cholecystectomy. Patient subsequently released as typhoid carrier.
40. B.S.	M 48	Negative	Enlarged, atonic, poorly emptying gall-bladder. Stomach and duodenum are negative.	Retro-peritoneal sarcoma in U.R.Q. No adhesions. Exploratory laparotomy. Pt. lived 18 months.

* For explanation of "Tuning Fork Response" see text.

† This was found true in 12 additional cases, namely nos. 45, 49, 54, 58, 59, 62, 64, 66, 68, 69, 73, and 84, although the cholecystogram in most instances had failed to demonstrate the presence of stones.

and in which a comparison was made of the relative accuracy of the tuning fork and roentgen-ray evidence as proved by the surgeon.

Of these 85 cases, table 1 * indicates that tuning fork and roentgen-ray evidence were in agreement and found correct by the surgeon in 42 cases or 49.4 per cent. Of these 42 cases the tuning fork yielded 27 positive and 15 negative tests.

* Because of lack of space, details of only 32 of the 85 cases reported have been included in the tables.

Table 2 indicates that the tuning fork test was correct and the roentgen-ray evidence for adhesions was incorrect as proved by the surgeon in 21 cases or 24.7 per cent. Of these there were 14 positive and seven negative tuning fork responses.

Table 3 indicates that the tuning fork test was correct as proved by operation, irrespective of the correctness of the roentgenological evidence, in 14 cases or 16.4 per cent. Of these there were eight positive and six negative tuning fork responses.

TABLE II

21 Cases in Which the Tuning Fork Test Was Correct and Roentgen-ray Evidence Was Incorrect as Proved by Operation

Case	Sex Age	T.F. Response	Roentgen-ray Evidence for U.R.Q. Adhesions	Operating Table Findings and Remarks
43. S.B.	F 72	*1, 2, 3	Poor visualization; no stone shadows; no irregularity in outline of gall-bladder or duodenum.	Trans. colon, duod., and greater curv. of stomach densely adherent to g.b. and liver. Small thick walled g.b.; 6 stones in common duct. Cholecystectomy and choledochostomy.
46. F.F.	M 45	1	Cholecystogram is normal except suspicious for gall-stones. G.I. series and barium enema are normal.	Small thick walled g.b.; no stones; adhesions between duod. and neck of g.b. Cholecystectomy. Appendectomy.
49. M.D.	M 56	1, 2	Non-visualized gall-bladder to dye test. No stone shadows. G.I. series normal.	Thick walled g.b. containing several stones; 1 stone in common duct; 1 stone perforated into duodenum; many adhesions between duodenum and g.b. Cholecystectomy and duodenal repair.
52. F.B.	M 39	1	Gall-bladder normal. No stones. Perfectly acting stomach. No deformities.	Chr. cholecystitis. Stones in g.b. and common duct. Adhesions between g.b. and duod. Cholecystectomy; choledochostomy. Appendectomy.
54. L.W.	F 50	1, 2	Pathological g.b.; no stone; no evidence of adhesions. Duodenum negative. Retrocecal appendix.	Thickened g.b. containing 2 stones. Duodenum densely adherent to g.b. and liver. Cholecystectomy; appendectomy. Death on 21st p.o. day.
58. M.S.	F 27	Negative	Pathological g.b. to dye test; no stone shadows; adhesions between liver or gall-bladder and duodenum.	Chronic cholecystitis; 7 stones; no adhesions. Cholecystectomy.
60. W.O.	M 36	Negative	Pathological gall-bladder. Hepatic flexure adherent to g.b. Duodenal adhesions (?)	Chronic cholecystitis. No U.R.Q. adhesions. Cholecystectomy.
62. R.S.	M 39	Negative	Normal gall-bladder. Duodenal ulcer. Adhesions (?)	No duodenal ulcer. Calculous cholecystitis. 18 stones. No adhesions. Cholecystectomy.

* For explanation of "Tuning Fork Response" numerals see text.

TABLE III

14 Cases in Which the Tuning Fork Test Was Correct as Proved by Operation, Irrespective of the Correctness of the Roentgen-ray Evidence

Case	Sex Age	T.F. Response	Roentgen-ray Evidence for U.R.Q. Adhesions	Operating Table Evidence and Remarks
65. E.T.	F 67	*1, 2	Non-visualized gall-bladder. No progress meal. Colon diverticulosis on barium enema.	Chr. cholecystitis, with dense adhesions between g.b., liver and duodenum. No stones. Cholecystectomy.
67. F.B.	F 59	1, 3	Prepyloric ulcer. No note regarding adhesions. No cholecystogram.	Chr. cholecystitis with adhesions between g.b., duod. and transverse colon. Pancreatitis. No gastric ulcer found after gastrotomy. Cholecystectomy.
68. K.M.	F 61	1, 2, 3, 4	Non-visualization of g.b. to dye test. No stones. No note regarding adhesions. No progress meal.	Gangrenous g.b. adherent to colon and duod.; adhesions, also, between liver, colon and duodenum. Many stones in gall-bladder. Cholecystectomy; choledochostomy.
69. I.A.	F 46	1	Non-visualization to dye test. No stone shadows. No progress meal.	Tense, thick walled gall-bladder adherent to duodenum. 2 stones in gall-bladder; 1 in cystic duct. Cholecystectomy.
71. E.W.	F 55	1	Cholecystogram shows negative shadows in a gall-bladder preserving good function. No progress meal.	Thick walled gall-bladder adherent to duodenum and containing 6 stones. Cholecystectomy.
73. L.L.	F 19	Negative	Non-visualization to dye test. No stone shadows. No note regarding adhesions.	Tense, distended g.b., opaque walls; 4 stones in g.b.; 2 in cystic duct; 4 in common duct. Cholecystectomy; choledochostomy. Chemistry of stones: 95% cholesterin; 5% calcium bilirubinate.
74. R.R.	M 52	Negative	Retrocecal appendix. Sigmoid colon adherent to cecum. No reference to U.R.Q. adhesions.	No U.R.Q. adhesions. Normal g.b. Appendix not found after 90 minutes' search. Sigmoid colon was not adherent to cecum.
76. F.C.	M 39	Negative	Pathological g.b., normal duodenum, non-visualized appendix. No note regarding adhesions.	No U.R.Q. or other adhesions. G.B. visibly and palpably normal. Appendix contained fecalith. Appendectomy.

* For explanation of "Tuning Fork Response" numerals see text.

Table 4 indicates that the tuning fork was incorrect as proved by operation, irrespective of the correctness of the roentgenological evidence, in eight cases or 9.4 per cent. Of these the tuning fork yielded five positive and three negative tests.

In the aggregate, therefore, the tuning fork test was proved correct in 77 cases or 90 per cent. The incidence of positive to negative tuning fork

TABLE IV

8 Cases in Which the Tuning Fork Test Was Incorrect as Proved by Operation, Irrespective of the Correctness of the Roentgenological Evidence

Case	Sex Age	T.F. Response	Roentgen-ray Evidence for U.R.Q. Adhesions	Operating Table Findings and Remarks
78. M.D.	F 29	*1	Normal cholecystographic response. No progress meal.	Surgeon reports: "Pathological gall-bladder. No adhesions." Cholecystectomy.
79. S.C.	F 48	1, 2	Pathological, greatly enlarged gall-bladder. No note regarding adhesions.	Surgeon reports: "G.B. enlarged, slightly thickened, non-adherent, contained no stones." Cholecystectomy.
80. M.F.	F 47	1, 2	Normal Graham test response. No progress meal. No irregularity in g.b. outline.	Surgeon reports: "G.B. perfectly normal. No adhesions. No stones. No abdominal pathology. Retrocecal appendix, but not in bad condition." Appendectomy.
81. J.T.	M 66	1, 2	Pyloric carcinoma; duodenal adhesions; pathological gall-bladder.	Carc. of pylorus. Normal g.b. No adhesions. Post. gastrojejunostomy. Death in 2 days.
82. H.K.	F 43	1	"No roentgen-ray evidence of pathology of stomach or duodenum except for duodenal adhesions to a definitely pathological g.b. which may contain stones; fixation of cecum."	Surgeon reports: "We felt this pt. had g.b. disease partially based on our roentgen-ray dept. report of a deformity of the stomach, but at operation the g.b., stomach and duodenum were normal." Closure.
83. E.M.	F 49	1, 2	Pathological cholecystogram. Suggestive evidence for U.R.Q. adhesions involving gall-bladder.	Thick walled, non-adherent g.b.; no stones; dense adhesions between transverse colon and abdominal wall. Cholecystectomy.
84. F.J.	M 34	Negative	Poorly visualized g.b.; no stone shadows; normal progress meal response.	G.B. firmly adherent to duod. and containing several stones; 2 duodenal diverticula. Cholecystectomy.
85. M.K.	F 64	Negative	G.B. not visualized to dye test. Faint mottling to suggest stones in gall-bladder and in cystic duct.	Surgeon reports: "G.B. shows chronic inflamed and thickened walls. It contained several calculi and was adherent to adjacent structures." (Note: surgeon did not specify to what structures.) Cholecystectomy. Appendectomy.

* For explanation of "Tuning Fork Response" numerals see text.

responses was 5.4 to 3.1. Both varieties were equally accurate, percentage wise.

COMMENT

In these tables the tuning fork response is entered as a numerical figure according to the following interpretative code:

Numeral I suggests adhesions between the gall-bladder and the pyloro-duodenal segment, because the T. F. response was positive between the right subcostal margin and the epigastrium (see technic of performing test).

Numeral II suggests adhesions between the liver and the pyloro-duodenal segment because the T. F. response was positive between the liver and the epigastrium.

Numeral III suggests adhesions between the gall-bladder and the colon (usually the hepatic flexure) because the T. F. response was positive between the right subcostal margin and the cecum.

Numeral IV suggests adhesions between the liver and the colon, because the T. F. response was positive between the liver and the cecum.

In examining these tables, the reader will also note that the roentgen-ray evidence and the operating table findings are reported only in abbreviated summary in order to save space. In doubtful cases, wherever possible, the author has thrown the weight of evidence against his test and in favor of roentgen-ray.

In tables 3 and 4 the reader will note the author's inability correctly to appraise the roentgen-ray evidence without appearing biased. A study of these tables will explain why.

In order further to conserve space, the author has reduced, in the text, tables 1, 2 and 3 to a report of eight cases which represents a sampling of the total number in each group.

Equipment for Tuning Fork Auscultation. The equipment necessary for this test is simple and inexpensive. The examiner, in addition to possessing good hearing sensitive to tone, requires only a stethoscope and a tuning fork.

The author has found that a bell type stethoscope 26 inches over all is desirable, for reasons subsequently stated. This means approximately 18 inches of rubber tubing, the last six inches of which should be a single tube.

The tuning fork should be a large size G sharp of 410 vibrations. The standard dimensions of this fork are 7 inches over all; 4.5 inches from tip of prong to fork, and 2.5 inches from fork to tip of stem. Each prong is $\frac{7}{16}$ inch deep and $\frac{1}{16}$ inch wide. The author has found by experience that the stem of this standard fork is too short to be held comfortably without some portion of the fingers or hand touching the abdomen. Such contact will give false readings because of surface conduction of sound. To overcome this the author has lengthened the stem, by welding, to an over all of 8.5 inches.

The extra long rubber tubing on the stethoscope is also important because it permits the examiner, when standing at the left side of the recumbent patient, to have sufficient length comfortably to transfer the bell of the stethoscope from the patient's left epigastric region to his lower right quadrant.

General Principle Underlying Test. The underlying principle of the test is the conduction of or transmission of a tuning fork note from one hollow

organ to another hollow organ, for instance from gall-bladder to stomach or duodenum; or from a solid organ to a hollow organ, for instance from the liver to the colon. This is possible, however, only if the two organs are in permanently close relationship to each other, that is bound to each other by adhesions.

Ellison [2] discusses the mechanics or physics of the test as follows: "When adhesions unite the pyloro-duodenal segment to the under surface of the liver or to other structures, such as the gall-bladder, which are in anatomic union with the liver, there is formed a continuity of anatomic structure between the liver and the walls of the stomach. If now the stem of the vibrating tuning fork is placed over the liver, the vibrations are transmitted directly from that organ to the walls of the stomach. The air bubble, which in the dorsal position lies in the left hypochondrium, acts as a resonator for the vibrations, amplifying them so that they can be heard by the overlying stethoscope. Mere apposition of structures does not produce the same sharp clear note, because the vibrations are dampened in passing from one structure to the other."

Technic of Performing the Test. The patient lies comfortably and evenly on his back. The examiner stands at the left side of the patient. The examiner places the bell of his stethoscope over the patient's epigastrium so that it occupies a portion of the topographical region of the patient's stomach. (See illustration.)

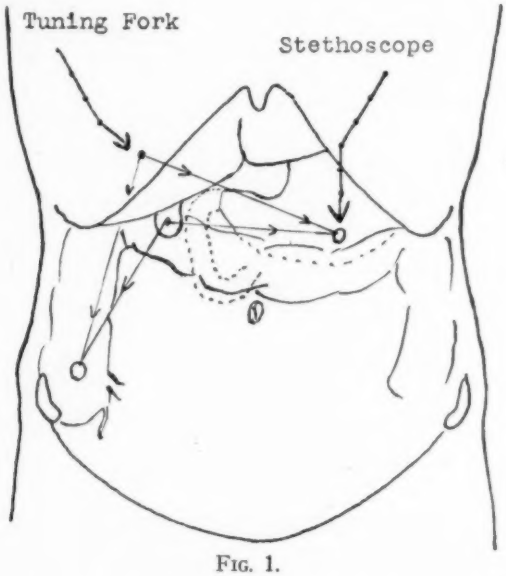

FIG. 1.

The examiner now smartly taps the tuning fork (preferably on his heel) and places its butt or stem close to the bell of the stethoscope. The musical note which the examiner will hear will be that given off by the patient's stomach. This musical note hereafter will be referred to as the 'gastric note.'

By means of "tuning fork auscultation" the examiner can then rapidly map out the size, shape and position of the stomach much the same as if he were attempting to do so by ordinary percussion or by auscultatory percussion. To do this the examiner first brings the stem of the vibrating tuning fork upwards, inch by inch, from various points in the lower left quadrant and towards the bell of the stethoscope. The reappearance of the 'gastric note,' clear and distinct, will indicate that the stem of the tuning fork has reached the lower border of the stomach. Second, the lateral border of the greater curvature can similarly be determined by bringing the stem of the vibrating tuning fork inwards from the splenic region. Third, the smaller area of the lesser curvature which lies below the costal margin can be best delineated by bringing the vibrating tuning fork from the mid right subcostal region inwards toward the stomach. As each portion of the stomach is reached the same clear cut tuning fork 'gastric note' will reappear. The pyloro-duodenal segment, representing some portion of the pyloric region and the duodenum, will also be found to lie within the third zone above described for outlining the lesser curvature. These are normal or negative tuning fork responses because they outline the average normal boundaries of the normal stomach.

Let me now discuss, equally briefly, the abnormal or positive tuning fork responses. It would be abnormal, and pathological in the sense of suggesting the presence of adhesions, if the examiner were to find that the clear cut 'gastric note' could be heard well beyond the normal boundaries of the stomach.* To be more specific as to possible adhesion formation and its location, there are four principal groups which the examiner should seek to identify: first, adhesions between the gall-bladder and the stomach or duodenum (the pyloro-duodenal segment); second, adhesions between the liver and the pyloro-duodenal segment; third, adhesions between the gall-bladder and the colon; fourth, adhesions between the liver and the colon.

Group I. Determination of adhesions between the gall-bladder and the pyloro-duodenal segment.

Using the same technic as just described for outlining the third zone or lesser curvature area, when the examiner can hear the 'gastric note' clearly and loudly below the right costal margin and laterally as far as or beyond the tenth rib, this should be considered abnormal. This would be presumptive evidence that some portion of the gall-bladder and some portion of the pyloro-duodenal segment are adherent. This notation of the tenth rib is arbitrary. It will not, of course, apply to a gall-bladder abnormally situated close to the spinal column as frequently occurs in a ptotic subject and is often thus demonstrable by cholecystogram.

Group II. Determination of adhesions between the liver and the pyloro-duodenal segment.

The examiner continues to keep the bell of the stethoscope over the stomach area in the left epigastrium, but now varies the technic by placing

* Ptosis and atony (dilatation) of the stomach might also be suggested as abnormalities.

the stem of the vibrating tuning fork over the liver, that is above the right costal margin. In certain cases the examiner will find that the 'gastric note' will be transmitted equally clearly and loudly from this area. In such cases this would be presumptive evidence that some portion of the liver and some portion of the stomach or duodenum are adherent to each other. Otherwise it should not be possible to transmit tuning fork vibrations from or through a solid organ (liver) to a hollow organ (stomach). The wider the area over the liver from which such vibrations can be transmitted, the more dense and widespread have been the adhesions when visualized at operation. However, there are two exceptions. When the liver is considerably enlarged, especially its left lobe, this interpretation of the test may be inaccurate because of direct sound conduction. Second, the examiner must avoid stretching the skin between bell of stethoscope and stem of tuning fork, since this will produce surface conduction of sound.

Groups III and IV. Determination of adhesions between gall-bladder and colon, and between liver and colon.

In the foregoing description of determining adhesions between the gall-bladder or liver and the pyloro-duodenal segment there is one major error that must be eliminated. This arises from the fact that in many cases the middle third and left third of the transverse colon may lie in juxtaposition to the stomach. Therefore, with the bell of the stethoscope placed over the stomach, as I have already described, it may also lie over some portion of the transverse colon. It would do so in non-coloptotic patients. With this in mind, and with the vibrating stem of the tuning fork alternately placed below and above the right costal margin, let us now suppose that in a given patient the examiner clearly hears this presumable 'gastric note' transmitted from the gall-bladder or liver region to the epigastric region over which he has placed his stethoscope. Why could not this be a note transmitted from the gall-bladder or liver to the *colon* instead of to the stomach?

Fortunately it is quite simple to decide whether the musical note thus heard is solely colonic and not gastric and the examiner proceeds as follows: If he places the bell of the stethoscope over the first portion of the ascending colon (that is in a position slightly above and to the right of the classical McBurney point) the tuning fork note given off from that region obviously should emanate from the colon rather than from the stomach. Next, if he places the stem of the vibrating tuning fork alternately under and over the right costal margin a definitely positive response will strongly suggest that adhesions are present between some portion of the colon (usually the hepatic flexure) and either the gall-bladder or the liver.

But a second possible error of interpretation remains to be eliminated. In the event that there are adhesions between gall-bladder and liver to *both* the pyloro-duodenal segment and the colon, why could not the note which the examiner has so clearly heard be transmitted to both stomach and colon? This, too, is easy to differentiate by the following maneuver. With the vibrating tuning fork placed alternately below and above the right costal

margin the examiner first auscultates over the epigastric region and then quickly transfers the bell of the stethoscope to the ascending colon near the McBurney point. If the musical tuning fork note is heard with equal clarity and definite positiveness at *both* positions this would be presumptive evidence that adhesions exist between the biliary tract and both the pyloroduodenal segment and the colon. However, if the musical note is clearly heard in the epigastrium only, the possibility of adhesions between colon and biliary tract is thereby eliminated; and vice versa if heard only in the region of McBurney's point.

In the average normal abdomen the distance, topographically, between the gall-bladder and the indicated position of the stethoscope over the stomach (see illustration) is approximately the same as the distance between the gall-bladder and the cecum. This would make the distance between the gall-bladder and stomach, the gall-bladder and cecum, and the stomach and cecum equidistant like a triangle. Therefore, no error in interpreting the intensity of the tuning fork note should occur because the stethoscope might be nearer to it in one location than in the other.

Caution and Advice to Beginners. Changing the bell of the stethoscope from one position to the other must be done rapidly and the examiner must remember that the intensity of the sound is constantly lessening with each instant of elapsed time and that this factor may modify his interpretation. Another counter-check may be made by revibrating the tuning fork each time the position of the bell of the stethoscope is altered. The latter may be better technic for the beginner who by practice, supplemented by operating table observation, will quickly learn what may have caused a misinterpretation of his findings and thus will teach him how to guard against repeating his mistake.

Tuning fork auscultation for adhesions is not an exact test that can be measured by a graph or a mathematical or chemical formula. It has a large degree of "personal equation" similar to that required in expertly palpating the abdomen, and much greater than that required accurately to record a blood pressure ratio or to do a complete blood count. It is a test whose accuracy will increase with experience cross checked by operating table inspection.

There are several errors in technic to be avoided. While applying the bell of the stethoscope and the stem of the tuning fork to the abdomen the examiner should push them toward each other. This relaxes the skin. Do not pull them away from each other. This will stretch the skin and will thus produce a "false positive" by surface conduction of sound. This is a common error and can be easily proved by alternately relaxing and stretching the skin between stethoscope and tuning fork.

A second and similar error will occur if the fingers holding either instrument are allowed to touch the abdomen. It is to guard against this that the lengthened tuning fork stem and lengthened stethoscope rubber are required, the measurements of which I have recorded earlier.

A third error will occur if the examiner stands at the right of the recumbent patient. In this position the prongs of the tuning fork will come too close to the tubing of the stethoscope and thus falsely transmit the sound. Try it and see.

A fourth and important error is one of omission. The test should be repeated at least twice and preferably on different days, and it should always yield the same result—a clean cut positive or a clean cut negative. This will guard against a "false positive" being produced by a peristaltic wave carrying the duodenum or the hepatic flexure of the colon, for example, into juxtaposition with the gall-bladder at the very instant the examiner makes the test.

Should the patient happen to have an inlying duodenal tube in stomach or duodenum at the time "tuning fork auscultation" is being made the positiveness of the test will be increased by injecting through the tube one or two ounces of air. This appears to act as a sounding board.

Let me again remind the beginner that he will make fewer errors if he goes on record with only clean cut positive or clean cut negative responses. There are intermediate readings that can be made with experience, but it is better for the reader to learn them himself than to be told.

Any surgeon with an active abdominal service can quickly check for himself the accuracy of this test by adding it to his routine examination of all patients whose abdomens he proposes to open, provided he plans visibly to inspect the upper right quadrant. Intraabdominal palpation of finer adhesions is often unreliable. Visible inspection will guard against this error decreasing the accuracy of tuning fork auscultation. With practice the test can be done readily in five minutes. It cannot be hoped that a beginner can achieve such a high percentage of accuracy with this test in his first group of cases any more than such accuracy can be expected in the hands of an inexperienced roentgenographer or of a novice with any new tool.

The accidental manner in which the author stumbled upon this test in 1911 was described in his original article.

Comment

The author has noted three different points of view regarding the value of this test.

First, that of the expert roentgenographer who is meticulous about every detail of his work. Such a one has a sufficiently competitive spirit to make him jealous of any one who can challenge the diagnostic accuracy of himself and his apparatus. For 15 years or longer Dr. Willis F. Manges, Professor of Roentgenology in the Jefferson Medical College, and I had been in friendly competition in detecting upper right quadrant adhesions. Prior to his untimely death (1936) Dr. Manges told me that, according to his score

card, my tuning fork test was 14 per cent more accurate than his beloved machine.

Second, there has been the surprised attitude of the operating surgeon when he has confirmed my preoperative diagnosis of upper right quadrant adhesions or their absence. Especially was this the case when my tuning fork diagnosis differed from the roentgenologist's report upon the accuracy of which he had come to rely.

Third, there was the general attitude of indifference on the part of the occasional doctor who was apt to say: "Well, suppose the patient does have upper right quadrant adhesions. What of it? How does it help you or the patient if you can recognize them preoperatively?"

I reply that it has helped me or the patient in three ways.

It has helped me more accurately to select for surgery the patient who requires surgery. The preoperative knowledge that adhesions involving the upper right quadrant actually exist is important because adhesion formation so frequently accompanies chronic gall-bladder disease and chronic gastroduodenal disease. This is the kind of disease that will be best eradicated or controlled by appropriate and skillful surgery. This test is more accurate in securing such information than is roentgen-ray, and far more so than intuitional guesswork.

Second, such information is important to me and to my patient because whenever adhesions are cut they are apt to reform. This is a bête noir to the surgeon, but a far greater one to the patient because their reformation tends to produce postoperative morbidity and suffering. Remembering this, the doctor is in a better position to plan the immediate postoperative care (narcotics, diet step-up, duration of hospital stay), and the longer 'follow up' with a skill personalized to his knowledge of his patient and his disease.

Third, such information is vastly important to the patient and to his attending physician because the presence of adhesions greatly increases the technical difficulties of the operation. This imposes a responsibility upon the physician, and it should equally influence the 'occasional' surgeon, to make sure that such a patient gets the highest surgical skill that is available. All of the patients in this report were operated upon by surgeons of unquestioned skill and experience in this field of surgery. Even so, it still shocks me out of my complacency to recall so many patients who failed to recover. The shock of such a death to the family and to the referring physician is not so great if the patient is found suffering from cancer. This was found present in six of the 11 deaths and raised the total mortality to 12.9 per cent. The mortality in the non-cancer patients was thus reduced to 6.3 per cent. Surely, even such a mortality will be considered too high. And when I state that the surgeons who operated upon the large majority of this series of patients were Professors of Surgery, that fact alone emphasizes the seriousness of complicated upper right quadrant disease and suggests that a higher mortality would result in less skillful and experienced hands.

Summary and Conclusions

1. A diagnostic technic is described for determining the presence of adhesions in the upper right quadrant of the abdomen.

2. This test is simple, inexpensive and accurate. It is called "Tuning fork auscultation—a test for abdominal adhesions." It requires only a stethoscope, a tuning fork, good hearing and adequate experience.

3. The author presents 85 cases in which tuning fork auscultation was compared with roentgen-ray evidence of upper right quadrant adhesions and was then proved correct or incorrect by operating table inspection.

4. In this series of cases the test was found to be 90 per cent accurate, whereas roentgen-ray evidence was something less than 65 per cent accurate.

5. The method of performance, as well as the errors in technic, are fully described.

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ALLERGY TO INJECTABLE LIVER EXTRACTS; CLINICAL AND IMMUNOLOGICAL OBSERVATIONS *

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The last two or three decades have witnessed tremendous and far-reaching advances in therapeutics, in many instances specific in character. This has been particularly true in the case of highly potent injectable substances such as immune sera, hormones, vitamins, and such specific factors as the antianemic liver fraction. With the older types of materials allergic reactions such as asthma, urticaria or serum sickness were obtained and were not unexpected, since they contained a considerable quantity of the animal proteins which were regarded as an essential feature of the mechanism of the reaction. Later, it was shown that even such a pure substance as crystalline insulin is capable of producing allergic reactions, acting as an antigen irrespective of the animal source.

It is our purpose here to call attention to the importance and significance of reactions to one type of injectable substance, i.e., liver extract. Since the introduction of parenteral liver therapy in 1932, 29 authentic instances of allergic reactions to liver injections have been reported. Considering the number of persons who have received such injections the impression is created that these reactions are infrequent and unimportant. In view of the fact that we have had the opportunity of observing and studying eight patients with definitely corroborated findings of liver allergy and that five of these have come from one clinic (the Hematology Clinic of Northwestern University Medical School), it is not unlikely that this problem is more common and widespread than the medical literature depicts. The majority of the case reports do not give evidence of the necessary observations in order to ascertain the nature of this type of allergy, its course and its significance. It is because of these considerations that we are prompted at this time to record the findings and studies on this group of individuals.

Case Reports

Case 1. L. H., a 65 year old woman, was seen in the Hematology Clinic in the autumn of 1937, where a diagnosis of pernicious anemia was made. One c.c. of Reticulogen (Lilly) was injected on October 23 and on November 13. On December 11, 1937, fifteen minutes following the third injection of liver extract, she began to have itching of the palms of the hands and soles of the feet. This was soon followed by cough, dyspnea and wheezing. Epinephrine hypodermically caused a prompt subsidence of the attack. The subsequent injection of liver extract induced a

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similar reaction. On February 16, 1938, she was given one-half cubic centimeter of Reticulogen intramuscularly, which was followed by a severe attack of generalized urticaria, edema of the eyes and lips, and dyspnea with blood-stained sputum.

On February 19, 1938, she was seen in the Allergy Clinic. In addition to the aforementioned story she gave a history of urticaria and asthma of several years' duration as well as a description of symptoms of allergic rhinitis. A son had hay fever. To substantiate her chronic allergic complaints, routine cutaneous tests disclosed several marked reactions, particularly to cattle hair, hog hair and house dust. Cutaneous tests were made with 10 commercial injectable liver extracts, with positive reactions to all but one. By the intracutaneous method all antianemic liver preparations reacted, the reactions being obtained in as high as 1: 100,000 dilutions with some of the products. Most of these liver extracts were obtained from livers of beef or hog origin. A preparation of liver extract obtained from the horse also gave a positive reaction. Because of the implication that we might be dealing with a special antigen residing in a fraction of the liver which is common to all mammalian livers and because of the theoretical interest that is attached to the possibility of auto-antigens, it was thought advisable to investigate the reactivity of the antianemic fraction of human liver. Such a preparation was made and resulted in absolutely negative reactions, whereas extracts made from beef and hog liver by the same method gave positive reactions.

Tests made with the pressed juice of the pork and beef liver or with protein fractions in varying dilutions gave positive reactions, but required higher concentrations to produce them. Because of the possibility that the specific antigen might be due to parasites which infest the cow and the hog, tests were made with extracts of ascaris and tapeworm, with negative results. One-tenth c.c. of the serum from this patient was injected intracutaneously in several skin sites of a non-atopic individual. Subsequently these sites were tested with anti-pernicious anemia liver fractions and reactions were obtained with dilutions as high as 1: 1,000.

For a time the patient was given liver orally. The response being poor, it was thought advisable to attempt to immunize her sufficiently to be able to resume parenteral therapy. This was begun in October 1939, and continued irregularly until May 17, 1941, when a dose of 0.8 c.c. of the 1: 100 extract was reached. During the course of these immunizing injections the patient had many marked local reactions and several mild constitutional allergic reactions. Two intensive courses of histaminase orally did not alter the titer of skin response. At the last testing (August 19, 1941) her skin tests showed reactions to practically as high dilutions as they did three and a half years before.

Case 2. A. Q., a 52 year old woman, was seen in the Hematology Clinic in October 1938, where a diagnosis of pernicious anemia was made. She had 14 injections of liver extract (3 c.c. Lilly's, 1 c.c. = 2 U.S.P. units), the first ones being given frequently and the later ones every three weeks. A few minutes following the fifteenth injection, on May 13, 1939, she had generalized urticaria and vomiting. On July 15, 1939, she had a moderate reaction from one-fourth cubic centimeter of the extract.

She was seen in the Allergy Clinic on August 22, 1939. No history of atopic disease in the patient or in the family was elicited. All the usual routine, cutaneous tests were negative. Marked cutaneous and intracutaneous reactions were obtained with several brands of injectable liver extracts in dilutions up to 1: 1,000. No reactions were obtained with horse liver in concentration as high as 1: 10. The human liver preparation gave a negative response. Liver juice, liver protein fractions, muscle protein fractions, and protein fractions from kidney and stomach did not produce positive reactions. The parasite extracts did not react. Passive transfer disclosed the presence of reagin, reactions being obtained with 1: 10 dilution of liver extracts.

On August 19, 1939, immunization was begun with Reticulogen and after several months a dose of .5 c.c. of the undiluted extract was reached. This dose was continued to August 24, 1940. During the process of immunization one systemic reaction occurred. Tests repeated on December 16, 1939, still showed marked reactions.

Case 3. M. T., a 68 year old man, was admitted to the Hematology Clinic on November 15, 1939 where a diagnosis of pernicious anemia was made. He received 10 injections of liver extract in a period of about four months, most of the treatments being administered at two week intervals. His first injections were of Lilly's concentrated extract (1 c.c. = 15 U.S.P. units) and the later injections were of Reticulogen (1 c.c.= 20 U.S.P. units). On May 18, 1940, a few minutes after his eleventh injection of liver extract, he complained of itching in the ears and palms of the hand and tightness in the chest. He was seen in the Allergy Clinic on May 28, where he gave an additional history of autumnal hay fever of 20 years' duration. Of all the routine skin tests made ragweed pollens were the only positive reactors. Several injectable liver extracts gave definite cutaneous reactions. The horse liver extract also gave a positive response. Protein fractions of beef and pork liver as well as protein fractions of the muscle tissue of these animals failed to give reactions. Tests made with the injectable liver extracts were still strongly positive six months later. On January 14, 1941, one-half c.c. of an outdated Lederle liver extract (1 c.c. = 15 U.S.P. units) was administered. A constitutional reaction resulted. On January 18, 1941, a reaction was precipitated by 0.1 c.c. of the same extract. The patient has not returned for observation since that time.

Case 4. P. P., a 43 year old male, a private patient, had been taking injections of Lederle's liver extract (1 c.c. = 15 U.S.P. units) at three week intervals for a period of 13 months for pernicious anemia. The last injection resulted in a generalized urticaria occurring within five minutes. An inquiry into his past history disclosed the fact that he had had a siege of urticaria 10 years previously. Tests were begun on December 12, 1939. All commercial liver extracts gave strong reactions. This included preparations of beef, pork and horse origin. The protein extracts of the beef and pork liver, as well as the protein extracts of the beef and pork muscle gave negative responses. The extracts of ascaris and tapeworm did not react. In spite of the skin reactions he was able to tolerate continued injections of a special beef liver extract (Lederle, 1 c.c. = 15 U.S.P. units).

Case 5. W. H., a 46 year old male, was seen in the Hematology Clinic in July 1940 where a diagnosis of pernicious anemia was made. After a series of injections of Reticulogen, consisting of daily small doses followed by three injections at intervals of three weeks, a reaction occurred on November 14, following an injection of 1 c.c. of the preparation. The symptoms consisted of itching of the hands and thighs, marked weakness and nausea. He was seen in the Allergy Clinic on December 21. There was no personal or family history of atopy. Positive cutaneous and intracutaneous reactions were obtained with several commercial liver preparations, which included beef, pork and horse sources. The pressed juices of pork and beef liver reacted slightly. The proteins of pork and beef muscle gave no reactions. Reagins were obtained from the serum but precipitins were not found.

Following an interval of six weeks after his last therapeutic injection of liver extract, the treatments were continued without any constitutional effects.

Case 6. F. E., a 47 year old man, developed an itching rash after several months of liver injections (various preparations) for pernicious anemia. There was no history of atopy. Moderate positive cutaneous and intracutaneous reactions to several liver extracts were obtained. Tests with liver and muscle proteins were negative. This patient was able to continue with injections without further reaction.

Case 7. M. S., a 20 year old male, had been under observation in the Dermatology Clinic for a stubborn acne. A fraction obtained from an anti-pernicious

anemia liver extract and from crude liver extract (designated A.–1) and apparently containing no chemically demonstrable protein was given intramuscularly as a therapeutic procedure. After one series of treatments six months elapsed before the second series was begun. The first reaction occurred on the second injection of the second series, and consisted of urticaria and faintness. A similar reaction occurred on the third injection and following the fourth injection a severe attack of asthma ensued. Treatments were then discontinued and allergic studies were begun.

A history elicited the fact that the young man had had a perennial rhinitis for several years and also had what was probably midsummer and fall hay fever. Routine skin tests disclosed definite reactions to grass and ragweed pollens and to house dust. Positive cutaneous and intracutaneous reactions were obtained with numerous commercial preparations of liver extracts as well as with the special fraction with which he was treated. With some of the materials intracutaneous reactions were obtained with dilutions as high as 1 : 1,000,000. Lesser reactions were obtained with the horse liver preparation. The pressed liver juice and the protein fractions gave reactions, but in much lower concentration than with the non-protein fractions. Muscle and other organ protein fractions as well as the parasite extracts gave negative reactions. Reagins were demonstrated with 1 : 1,000 dilution of some of the liver antigens. Precipitins could not be demonstrated. Tests have been repeated over a period of eight months; the last made (July 15, 1941) showed no appreciable difference in the intensity of the skin reaction.

Case 8. J. P., a 68 year old woman, was under the care of Dr. Paul Shallenberger, for an anemia of undetermined nature. She had been receiving injections of liver extract (Reticulogen, 0.5 c.c.) at first weekly and then every 10 days. About two minutes following the sixteenth injection there ensued a reaction consisting of itching of the hands and feet, swelling of the tongue and throat and dyspnea, apparently without wheezing. The patient was referred to us for allergic tests which were made about three weeks after the constitutional reaction. Cutaneous tests showed decided sensitivity to several commercial brands of injectable liver extracts (beef, pork and horse). The beef liver extract and horse liver extract reacted less than the hog liver preparation. The protein-rich pork and beef liver juices, as well as the muscle preparations of these animals failed to react.

Analysis of Cases

Relation to Atopy. The question arises as to whether there is a relationship between this type of induced allergy and the presence of atopy (asthma, hay fever, etc.) in the patient. Harten and Walzer,[1] in their thorough review, find that in the total of 28 cases reported in the literature, seven were frankly atopic persons. There is the possibility, of course, that some of the others may have also been atopic and that not every author has seriously inquired about the presence of atopy or has failed to record it. In our series of eight cases, three had long established chronic atopic manifestations, and another had some recurring urticaria. It may not be entirely insignificant that these three frankly atopic persons have not been able to tolerate injections of full doses of liver extract even after long intervals or after prolonged periods of "desensitization."

Liver Injections Preceding Allergy. In all instances the reactions followed injections which were previously tolerated without any difficulty. The number of such injections preceding the first allergic episode varied from

two to about 15. A study of the original case records would indicate that a long interval between injections (three weeks), or a long period between series of injections favors the establishment of sensitization. In none of these patients were reactions initiated while they were receiving injections at intervals of one week or less.

Clinical Manifestations. Asthmatic reactions occurred in about half of the patients. Either itching and flushing of the skin or some form of urticaria or angioneurotic edema was manifested in practically all patients. Nausea, weakness and faintness were common complaints. As a matter of fact, the different allergic manifestations occurred often at different times in the same individual when repeated reactions were produced. There was a tendency for the lighter reactions to occur first and for the more severe manifestation to appear on the repetition of the injections. In the approximate order of increasing severity these manifestations consisted of itching of the skin, particularly of the palms of the hands, or flushing of the face; nausea and slight faintness; generalized urticaria and angioneurotic edema; asthma; and generalized reactions. Anaphylactic shock has been described by others.

Skin Tests with Commercial Antianemic Liver Fractions. In the reports included in the review of Harten and Walzer, 11 patients had been tested intracutaneously, with positive reactions in nine. In our series all patients gave the immediate whealing type of cutaneous (scratch) and intracutaneous reaction with the commercially prepared injectable liver extracts. A fairly large series of persons with other allergy gave negative reactions to these extracts. One patient who had a very mild constitutional reaction and who was able to continue with his liver injections failed to give positive scratch reactions but gave a fairly strong reaction to the 1: 100 extracts intracutaneously. His case is not included in this series. The volume of the intracutaneous injections never exceeded 0.02 c.c. Positive reactions intracutaneously were obtained in different patients in dilutions ranging from 1: 100 to 1: 1,000,000. In performing these tests a variety of commercial brands of liver extract was used and although positive reactions were obtained with essentially all of them there was some variation in the titer of the reaction. In all instances both the beef and pork liver extracts gave positive tests. The horse liver extract gave positive reactions in all cases tested but one, although the reactions to this preparation were usually weaker. No delayed, or alarming immediate local or general effects such as have been described previously followed the tests, presumably because very strong concentrations were not used when weaker ones gave definite reactions.

Skin Tests with Specially Prepared Extracts. A human liver extract was prepared in accordance with a standard method for separating the antipernicious anemia principle. This extract gave entirely negative reactions in two patients who were strongly sensitive to other liver extracts. In order to ascertain whether we were dealing with an organ specificity we made tests

with other liver fractions. The proteins precipitated from the macerated liver, and prepared as protein antigens are usually prepared for routine allergic tests, gave negative reactions for the most part. The same was true of the pressed liver juice, which, though extremely rich in proteins, gave little reaction on these patients. When positive tests were obtained with these products they were evident only in comparatively high concentrations. It was apparent that the preparations containing tremendous quantities of proteins had very small quantities, if any, of the antigen in question, whereas the preparations which failed to disclose any protein by chemical tests (some of the commercial liver extracts) had high concentrations of the antigen. The only patient who was an exception to this observation was Case 1 who reacted to the protein fractions in fairly high dilution. The nature of her allergy is further complicated by the fact that she gave strong reactions to cow and hog dander. It may be that in her case several separate allergies are involved, some previously existing and the others induced.

In all instances protein extracts of the muscle (meat) of beef and hog gave negative reactions. This is in conformity with previous reports.[2, 5, 6, 7] Protein extracts of kidney and stomach were tested in three patients and the only positive reactions were obtained in Case 1. Fractions of these organs prepared according to the method employed in preparing the antianemic fraction of liver gave moderately positive tests in Case 1 and negative in Case 4.

In four patients tests were made with extracts of ascaris and tapeworm. This was done because of the remote possibility that the curiously behaving liver antigen might originate from the infestation of some of the animals with these parasites. Negative tests were obtained in all.

Specific Antibodies. Of the patients reviewed by Harten and Walzer, eight who had direct positive skin reactions were tested by the indirect method (passive transfer) also. Of these, seven showed passively sensitizing antibodies.[2, 4, 5, 6, 7, 8, 9] In our series four patients were tested in this manner and all of them showed reagins specific for liver extract. That is to be expected, since a true immediate type of allergic reaction always displays passively transferable reagins if the titer of reactivity is sufficiently high. The sera of two patients were tested for precipitins to liver extract but no appreciable titer was found in either.

Clinical and Immunologic Course. The clinical course of these patients is somewhat varied. In four of these cases full therapeutic doses of liver extract could not be administered without reaction, after an interval of several months to three and one-half years following the initial reaction. In another (case 8) it is too early to say whether liver would be tolerated in the future, since the allergic reaction has occurred only recently. However, in view of the violent and serious nature of the reaction, such an eventuality remains in doubt. The three remaining cases were able to resume liver injections without any interfering reactions. The status of these patients who have been able to continue with liver injections is of

interest. Cases 5 and 6 had the mildest constitutional reactions and skin reactions of low degree. Both were able to continue with the standard liver extracts. Case 4 was changed to an extract made from beef liver and he has been able to tolerate this material. On his tests he had shown strong reactions to both pork and beef liver, the latter, however, being less in intensity. It is possible that this difference was of sufficient degree to enable him to tolerate the special beef liver extract.

TABLE I

Clinical Data

Diagnosis	Previous Allergy	Nature of Reaction	Anti-Pernicious Anemia Liver Fractions Beef or Pork	Results and Disposition
1. L. H. Age 65 Pernicious anemia Asthma Urticaria	Asthma Urticaria	Asthma and urticaria. Several repeated reactions in process of "desensitizing."	Positive scratch and intracutaneous reactions to all products as high as 1 : 100,000. First tests made 2/19/38.	Tests still strongly positive 3½ years after first tests. Only partial desensitization accomplished by repeated injections.
2. A. Q. Age 52 Pernicious anemia	None	Generalized urticaria and vomiting. Repeated mild reactions in process of "desensitization."	Positive scratch and intracutaneous reactions to most products. First tests made 7/15/39.	Desensitization continued intermittently for one year to August 24, 1940.
3. M. T. Age 68 Pernicious anemia Hay fever	Hay fever for 20 years.	Generalized itching and tightness in chest.	Positive scratch and intracutaneous reactions to several products. First tests made 6/15/40.	Tests repeated 12/28/40. Still strongly positive.
4. P. P. Age 43 Pernicious anemia	Urticaria 10 or 12 years ago.	Urticaria	Positive scratch and intracutaneous reactions to several products. First tests made 12/18/39.	Tolerating injections of beef liver extract.
5. W. H. Age 46 Pernicious anemia	None	Urticaria, nausea and weakness.	Positive scratch and intracutaneous reactions to several products. First tests made 12/14/40.	After discontinuing injections for six weeks, he was able to continue them without reactions.
6. F. E. Age 47 Pernicious anemia	None	Itching rash.	Positive scratch and intracutaneous reactions. Tests made 7/6/40.	Continued with injections without reactions.
7. M. S. Age 19 Acne Hay fever	Hay fever Perennial rhinitis	Urticaria and faintness on first two reactions. Asthma on third.	Positive scratch and intracutaneous reactions as high as 1 : 100,000. First test made 11/16/40.	Tests made 7/15/41 show no reduction in sensitivity.
8. J. P. Age 68 Pernicious anemia	None	Itching of skin. Angioneurotic edema and dyspnea.	Positive scratch reactions to several products.	Injections discontinued.

TABLE II

Immunological Data

A-1 Fraction	Anti-Pernicious Anemia Liver Fractions Derived from Other Species	Liver Protein Fractions and Liver Juice	Organ Extracts Prepared According to Anti-Pernicious Anemia Method	Muscle Protein Fractions (Beef and Pork)	Protein Fractions from Other Organs	Tapeworm and Ascaris	Other Reactions	Antibodies
1.	Horse—positive Human—negative	Positive, but weaker than anti P.A. fractions.	Kidney and stomach gave moderate reactions. Muscle, negative.	Negative	Kidney and stomach moderately positive. Muscle, negative.	Negative	Cattle hair, hog hair, and house dust	Reagin—positive
2.	Horse—negative Human—negative	Negative		Negative	Negative	Negative	Negative	Reagin—positive.
3.	Horse—positive	Negative		Negative			Ragweed	
4.	Horse—positive	Negative	Negative	Negative		Negative		
5.	Horse—positive	Slight reactions		Negative				Reagin-positive. Precipitins—negative
6.				Negative				
7.	Horse—moderately positive	Moderate reactions		Negative	Negative	Negative	Grass and ragweed pollens. House dust	Reagin—positive. Precipitins—negative
8.	Horse—moderately positive	Negative		Negative				

In four of these patients tests with liver extracts were made at various times and at the last testing they were found to be still strongly positive. This was the situation in Case 1 after three and one-half years, in Case 2 after 13 months, in Case 3 after six months and in Case 7 after eight months. The course of the skin reactivity of the remainder of the patients is not known.

Discussion

According to our experiences, allergy to liver extract is not as uncommon as is indicated from the relatively few cases reported in the literature. During the three and one half year period from the beginning of 1938 to the middle of 1941, we have given parenteral liver therapy to 48 patients with pernicious anemia in the clinic and in private practice. Of this number, six patients (12.5 per cent) acquired sensitivity to the commercial liver extracts. In view of the large number of persons, with or without pernicious anemia, who are receiving liver injections, it would seem that allergy to these preparations is a fairly common phenomenon.

It is possible that the common usage of the long interval method allows more ready sensitization. This would be in conformity with experimental work on hypersensitiveness in animals, with many observations on other types of induced allergy in man and with the histories of the patients described in this paper. There is also the possibility that we may be dealing here with a special type of antigen which sensitizes rather readily. Although we do not know the exact chemical nature of the antigen, it can be stated that in some way it is associated with antianemic principle.

The degree and seriousness of the allergic reactions vary widely. In general, there can be observed a definite relationship between these factors and the subsequent management of the patient. Those with marked constitutional reactions and high degree of skin sensitivity are generally unable to tolerate liver injections, even after considerable intervals.

The question arises as to the course available when a distinct allergic systemic reaction has occurred. Several solutions of the difficulty are possible. As already noted, in some of the mild cases injections may be continued with no ill effects. In some instances this may be aided by a temporary discontinuance of the injections. In one case the difficulty seems to have been solved by a change to a liver extract derived from beef.* It is also possible that in the more difficult cases a course of desensitizing injections may produce a sufficiently high level of tolerance. It is quite definite, however, that in a number of instances of liver allergy therapeutic doses cannot be tolerated at any time. In such eventualities we must confine ourselves to the use of liver orally, which fortunately is usually well tolerated.

The observations recorded in this communication and some of the details omitted for the sake of simplicity open up a number of controversial im-

* Beginning a few months ago Lederle's Concentrated Liver Extract (1 c.c. = 15 U.S.P. units) is being prepared exclusively from beef liver.

munologic questions. We feel that this is not the place to discuss all of these aspects but several of the more fundamental deserve comment. There can be no question that in this group of allergic reactions we are dealing with a special antigen which is not the ordinary species specific antigen. The organ tissues other than the liver did not contain such an antigen (with the exception of one special case). The pressed liver juice, rich in proteins, contained only a trace of this antigen. The precipitated liver proteins contained practically none of this reacting substance. It is quite apparent, then, that this antigen is neither the ordinary liver protein nor closely bound to it. The antigen is not species specific, nor strictly organ specific, but it is specific as a special organ fraction, bound up with the antianemic fraction.

A fraction of liver could be further isolated by precipitation of some of the commercial injectable liver preparation with acetone. This precipitate, when subjected to chemical analysis by Professor Chester A. Farmer,* showed no trace of protein discernible by the finest chemical tests and no evidence of the presence of carbohydrates, but it did contain 10 per cent of nitrogen, probably mostly in the form of amino acids. It is of interest to note that this protein-free (chemically) substance was able to give specific intracutaneous reactions in dilutions as high as 1: 1,000,000. Some of the commercial liver extracts also failed to show proteins by chemical tests. This suggests another interesting point of departure in the concept of the nature of antigen and in the mechanism of allergy. Immunologically specific immediate whealing reactions are elicited mainly by protein antigens. In recent years some specific carbohydrate fractions have also been shown to possess this property. Drugs and simple chemicals can cause typical and violent constitutional reactions of the atopic variety (asthma, hay fever, etc.) but as a class they are known to be devoid of skin reacting properties. In these liver fractions, however, we seem to have an antigen which is essentially free of protein, is capable of producing violent atopic manifestations, and readily produces immediate cutaneous reactions. This would suggest the need for more extensive study of antigens from the point of view of other concepts than the orthodox protein theory.

The criticism may be presented that our experiences do not necessarily demonstrate a special organ specificity, but that the process of extraction of the antianemic principle may constitute a better method of purifying or concentrating the usual species or organ antigen. The following brief reports are an answer to such possible criticism.

M. H., a 19 year old girl, was seen with the complaint of asthma of four years' duration. Among other reactions there were definite cutaneous responses to the proteins of beef and pork (muscle) and horse serum. The pressed juice of beef and pork muscle, as well as the juice of the livers of these animals, reacted intracutaneously in dilutions of about 1: 100,000. Several of the brands of liver extract employed for pernicious anemia gave reactions from weakly positive to definitely negative. An anti-pernicious anemia fraction obtained from horse liver gave a nega-

* Chairman of the Department of Chemistry.

tive test. It is clear, then, that here we are dealing with a totally different type of allergy, one having to do with species specificity, confined to no particular organ (muscle, liver or serum), apparently residing in the protein fraction, and being absent or present only in traces in the antianemic liver fraction.

Mrs. N. F., a 47 year old housewife, consulted us because of an allergic rhinitis and asthma of about 20 years' duration. In addition to other more significant skin reactions she showed positive cutaneous tests to beef and lamb. The unpurified extract of beef liver gave strongly positive reactions whereas the pork liver failed to react. The anti-pernicious anemia fractions gave questionable reactions. As in the preceding instance here we are apparently dealing with a species specificity rather than an organ fraction specificity.

Further experiments suggest themselves for the more complete clarification of this type of allergy. Liver fractions from widely divergent animal sources, such as chicken and fish should be tested. The antigenic effect of the antianemic fraction in the laboratory animal deserves investigation. The determination of the exact chemical nature of this antigen in anti-pernicious anemia extracts may point the way to a better understanding of the characteristics of antigens in general. And finally, the preparation of other fractions from animal and vegetable sources by methods employed in the preparation of this liver antigen may prove to be a generally useful method of isolation of antigens. Some of these suggested experiments are under way, but their discussion here is at present unwarranted.

Summary

Allergic reactions to injections of liver extract are reported in a series of eight cases, six of whom were receiving the material for pernicious anemia, one for anemia of undetermined nature and one for acne. It is suggested that this type of induced allergy is not uncommon. Cutaneous and intracutaneous tests with various fractions of liver and other organs of several species of animals indicate that this type of allergy has neither a species specificity, nor an organ specificity involving the usual protein antigen. The specificity appears to be limited to a special fraction of an organ (liver) not bound with the ordinary protein fractions but associated with the antianemic fraction. In addition to the practical importance of the occurrence and the management of this type of untoward result of liver therapy, attention is called to the potential immunologic significance of the demonstration of an antigen residing in a fraction of an organ tissue. Attention is called further to the possible significance of the demonstration of a highly potent antigen containing no protein and yet exciting skin reactions.

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CARDIAC PROBLEMS IN WAR TIME*

By PAUL D. WHITE, F.A.C.P., *Boston, Massachusetts*

I SHALL not discuss the cardiac problems in war time which are also those in times of peace and which include the vast bulk of all the problems that both civilian and military doctors have to face, such as the diagnosis of coronary and rheumatic heart disease, the treatment of angina pectoris and myocardial failure, acute pericarditis, and arrhythmias. I shall plunge at once into the specific problems bearing on the heart in this year 1942.

First, a brief word about the cardiologist himself. His rôle is not a simple one. If a civilian, he is overburdened with the cardiac responsibilities of the folks at home, young and old, in caring for their acute and chronic illnesses and in helping to weed out from among the candidates for Navy and Army those whose hearts are unfit and to pass for military service those under suspicion, whose hearts are really fit. If a military man, he has left his hearts behind him. Theoretically, and practically too, most cardiologists who have donned the uniform have little of their specialty to perform, in the recognition and care of an infrequent cardiac patient who develops de novo or who has slipped through the examiners into service. Many of my cardiological friends in Army or Navy, though often busy, only in rare instances are busy with heart patients. They direct general medical services in camp or station hospitals or run infectious disease wards or even help the surgeons or the experts in other fields such as venereal disease. This is, as it should be, for awhile at least, a broadening influence for them and useful for Uncle Sam. On the other hand, those of us still in civilian clothes are working very hard trying to keep up with the acute and chronic problems of the cardiac patients at home. We are envious of our fellows who are likely to sleep well most nights and yet at the same time pleased that we can continue to practice what we have been trained to do, even though it is under pressure. However, it looks, hopefully now, as if in not too long a time there will be relief for both groups, at the end of the war. Perhaps some cardiologists will come back with new interests to other fields of labor, but the cardiovascular problems still beckon and presage the need of extensive tillage in the future.

The second problem which I would present largely concerns those of us who remain at home. Able but aging men, and women too for that matter, have been called back from leisurely retirement to the strenuous days of business, professional, or military duties. Some of them are working much harder than they had ever worked before when they were many years younger. And some of them have hearts and arteries that are not capable

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of this strain, crippled by newly acquired or aggravated angina pectoris or by dilatation and failure of a previously overburdened heart in the case of hypertension or valvular disease. This has happened to a number of my own patients, despite attempts to avert trouble. It is in many cases a true hazard of war but in other cases it is more or less preventable. Both for the sake of the community and the nation, and for the individuals themselves we must try as best we can to protect them against unnecessary overstrain—we can help plan their programs. Some of them, however, will succumb no matter what we do; they are the unsung heroes and martyrs of the war.

I shall now pose four questions which concern both those of us who examine the registrants for the Army and those of you who have to do with them after they have been admitted as soldiers. They concern pulse rate, blood pressure, murmurs, and that condition of ill health called neurocirculatory asthenia. They remain as problems inadequately answered, but the airing of the problems and the expression of our personal opinions are assuredly worthwhile. So far as I am concerned today I speak as an individual and in no way officially.

The *pulse rate* is still a stumbling block. What is the range of the normal, which may be acceptable for military service? There are a number of ideas about this. For example, at present Mobilization Regulations 1 to 9 state that a truly persistent heart rate of 100 or over should be considered a cause for rejection. Some examiners follow this recommendation quite literally. On the other hand, some believe that a heart rate of 120 at the time of examination even on repeated examination, is quite all right. Lewis states that "emotion raises the pulse very easily, a persistent rate of 120 or even 140 during a single and brief examination has little significance." He also refers to drugs occasionally used to raise the rate, cordite and thyroid. It may not be possible to reëxamine some of these men at leisure or at least adequately, and so a good many have probably been rejected for an unimportant tachycardia. Much less has been said about bradycardia, as slow rates are much more readily acceptable. For example, U. S. A. MR 1 to 9 state that a pulse rate of 50 or under is acceptable provided it is proved to be the natural pulse rate of the individual, and yet heart rates around 40 per minute have been seriously questioned.

I would like to give my own experience with normal heart rates, first as to tachycardia. Some years ago I counted the pulse rate of six possible winners of the Ashland to Boston Marathon run at the starting line immediately before the race began and at the finish line immediately after they had completed the 25 mile distance. Their pulse rates before and after were respectively as follows: 64 before and 136 after, 86 and 120, 60 and 140, 62 and 108, 80 and 80, and last but not least 118 and 110. The last man whose pulse rate was the fastest by a considerable margin at the starting line was the easy and comfortable winner of the race in close to record time and his heart rate actually came down during that gruelling test. That experience taught me a lot, as did the observation of a fall in heart rate of a

nervous but husky Marine candidate in my own quiet office in the course of an hour from 130 to 65 per minute, proved by electrocardiogram.

Recently I have had the opposite or slow heart rate range brought to my attention. Some of you may have noticed a letter on the extreme bradycardia of distance runners in the *Journal of the American Medical Association* of a few weeks ago. Three perfectly normal champions of long distance running, a miler, a two miler and a Marathoner, and an aviator had proved basal heart rates of 37, 38, 35, and 38 per minute respectively. Doubtless there are more that I haven't heard about, and pulse rates in the forties are common among athletes. Only the other day a professional man aged 62 came into my office for a check-up after an excellent recovery from a myocardial infarction. His heart rate was 43. I thought that perhaps this slow rate might have resulted from the coronary heart disease, but I also thought to ask him if by chance he had ever done any distance running in his youth and he answered "yes," that he had been captain of the Yale cross country team over 40 years before and had always had a slow pulse.

Thus my own conviction from simple clinical observation during the last 25 years is that the normal pulse rate, at rest or relative rest, even in outstanding athletes, has a tremendous range, actually from 35 to 118 per minute.

Next, the question as to *blood pressure* is harder. Opinions differ as to the upper range, particularly of the systolic level in a young man. MR 1 to 9, although setting a limit, allows freedom of interpretation and judgment about that limit; thus a cause for rejection is a "persistent blood pressure at rest above 150 mm. systolic or above 90 diastolic, *unless* in the opinion of the medical examiner the increased blood pressure is due to psychic reaction and not secondary to renal or other systemic disease." This question of the blood pressure remains for the day our most difficult cardiovascular problem, strictly as such, neurocirculatory asthenia only secondarily being a problem, though a hard one, for the cardiologist.

How high may the blood pressure normally rise on excitement, at physical rest, and not represent a threat for the future? No one has adequately answered that question as yet. One can certainly be more liberal with the systolic level. Lewis, for example, has been very much so. He wrote in 1940 that "single readings of systolic blood pressure up to 180 mm. Hg in soldiers who are out of bed are not of much value in diagnosing essential hypertension," that "readings of 230 and over are much more significant," that "readings as high as 180 are not infrequent in 'effort syndrome' cases, effort or excitement carrying readings to high points in these," and that "essential hypertension should not be diagnosed unless successive readings such as 180 to 200 have been recorded in the subject lying at ease and completely rested; preferably it should not be made until such readings have been taken with the subject in bed." But undoubtedly we should be much more concerned with the diastolic level.

Among the hyperreactors to excitement, to effort, to cold, and to drugs are

probably most of the hypertensives of the future. We must go beyond Lewis' attempt to diagnose clear cut essential hypertension at the time of the examination and try to weed out the cases which sooner or later will develop the condition, in 5, 10, 15, or 20 years and in a few rapidly developing cases even in a year or two, unless the pressure for manpower is excessive, and it has not yet reached that point. Why should we try to be so careful? In the first place because some of these hyperreactors come to grief rapidly, secondly because the strain of military service may in some cases accelerate or precipitate the process, and, last though perhaps not least, as the Veterans' Bureau constantly is reminding us, we taxpayers will be penalized in years to come to pay for the disability of men whose hypertension may have developed in service or can in any way be service connected. However, in the present state of governmental development here or elsewhere this last argument may not for the moment be so much a medical as a political problem, unless a radical change takes place from the medicopolitical status of the veterans after the first World War. Despite this gloomy foreboding concerning the probability of decision as to service connection of the dim and distant hypertension in veterans of the present war, we can and should do something about the problem, and not shut our eyes to it as too difficult. We can at least make studies which will be helpful for the future, even for future wars or at least for the future employment of the international military forces that will be needed to police the world for a generation or more to come.

It would, of course, be convenient to shut our eyes to the problem by omitting the taking of blood pressures altogether in the registrants inasmuch as not many true established hypertensives among these young men would thereby be admitted to service. We need this very information, however, in projected studies which cannot be supplied by statistics from insurance or college or other groups despite the valuable hints from those sources. One study about to begin which we hope will bear fruit is to review the annual blood pressure and health records of our own military officers dating back to the days of the earliest routine blood pressure measurements. We hope that we may secure useful information about the future of men who start off with so-called high normal pressures in contrast to that of those who begin with low normal pressures.

Not only are we concerned with the health record of the men we admit to the Army and Navy but we are concerned with their efficiency record too. The efficiency of an army is more important in the final analysis than our ideas about its health, though of course, as a rule the two apparently go hand in hand. However, it has been suggested that men with high normal or even slightly elevated blood pressures are stronger and more alert and have more endurance, on the average, than those with low normal or slightly depressed blood pressures, say 150 to 160 systolic and 90 to 95 diastolic in comparison to 100 systolic and 65 diastolic. This may be so and perhaps the related question that has been asked is appropriate, namely "Do we want a long-lived

army or an efficient one?" But it is not so simple as all that, nor do we have the facts as yet.

Figures already gathered do indicate that among the youthful hyperreactors will be the hypertensives of tomorrow, but we don't know what percentage or which ones. One college follow-up showed only a minority still in the higher range ten or more years later, and we lack adequate military follow-up. Hence the proposed study.

Meanwhile what is the sensible thing to do about the blood pressure? I expect it is to follow the middle of the road. During 1940 and 1941 too many registrants were doubtless turned down all over the country for so-called hypertension. The interpretation of the figures was too literal and brusque, and I expect that we can salvage quite a few of those rejectees. Recently, on the other hand, with the letting down of the bars all around, it is probable that hypertensives, present and future, are slipping in too freely. I understand that we are not in such dire need of manpower as to admit these men as yet. We can still be choosy, especially with the older registrants, from 36 to 45, who constitute the greatest hazard and who illustrate perhaps what the status of the veterans now 20 to 30 years old will be in 1957. I was told recently that whereas 7 out of 10 registrants aged 20 to 28 are passed as physically fit, only 3 out of 20 of those aged 36 to 45 are so qualified. This important fact speaks for itself.

Shall we continue to use the figures for blood pressure in MR 1 to 9 of acceptable upper levels of 150 mm. systolic and 90 diastolic at rest or shall we raise them? It is my personal opinion that if we do raise them at all it shouldn't be by much. Perhaps under the excitement of the examination 160 might be acceptable as the upper limit of the systolic pressure, but I wouldn't raise the diastolic level much if any. I am dubious about even a 5 millimeter raise, that is, to 95. For the time being, with these remarks about the rules and our ignorance in general and in particular, the common sense of the examiners must be largely relied upon and that's about all I can tell you of my thoughts concerning this important subject of the range of normal blood pressure.*

The next problem that I shall speak of is that of *heart murmurs* among the candidates for Army and Navy. In 1940 and 1941 too many perfectly fit young men were being turned down because of the finding of inconsequential physiological murmurs, whereas relatively few cases of actual heart disease were slipping through when the finding of certain murmurs should have held them up. In recent months, however, the tide has turned, with the letting down of the bars, and men with real cardiac diseases are unfortunately being admitted in too large a number. Shortly after the A.E.F. reached northern Ireland, a medical friend of mine in one of the larger hospitals there wrote me about the dull but encouraging dearth of any cases of cardiovascular disease arriving in his wards; it was a rare and exciting

* It is quite probable that increase in blood pressure due to nervousness associated with increase in pulse rate is less important than increase in blood pressure with a slow pulse rate.

occasion when a congenital or rheumatic heart lesion came to light, usually mild and not too readily diagnosed. But only the other day when I visited a camp hospital the medical officers had lined up for me to see a group of men with very obvious valvular heart disease, who should never have been admitted at all, but who were passed recently, either because the examiner was deaf or tired or nonchalant about them. One of them was passed intentionally because his murmur was only a systolic one, a hangover from the casual disregard of murmurs that held for awhile during and shortly after the last World War, in part because of Mackenzie's needed reassurance about murmurs during the pressing demand for manpower for the British Army. That man's murmur, however, was a loud one at the apex, the heart was definitely though not greatly enlarged, and there was a perfectly clear history of rheumatic fever. It was really ridiculous to enroll him, simply on the basis of the timing of the murmur. Of course he was not in failure and his functional state was good, but there are two important reasons, nevertheless, why such cases should all be rejected, for combat service at least. In the first place, there is present structural heart disease involving heart valves and heart muscle which under the strain of war can develop arrhythmia, dilatation and failure, or even subacute bacterial endocarditis, no matter how fit the person seems to be at the moment. And secondly, there is the very definite hazard of recurrent rheumatic fever in these cases after exposure to infection with the hemolytic streptococcus, a far greater hazard than in those who have not previously had rheumatic fever or if they have had it, at least have not had permanent valvular deformity or cardiac enlargement resulting. Rheumatic fever, even in epidemics, can develop in the Army and Navy, but it will not be much of a problem if we weed out these obvious rheumatic cases at the source. I believe also, by the way, that if acute rheumatic fever does develop in service in a man without previous heart damage and is brief and leaves no residual effect on the heart it need not in every case necessarily be a cause for discharge from service.

What murmurs, then, are acceptable and what are rejectable? Let us take the latter first. All diastolic murmurs are abnormal and so are all loud or moderate persistent systolic murmurs at the cardiac apex, aortic valve area, and at the left of the lower sternal border. So too are very loud or even loud pulmonary valve systolic murmurs if persistent in all body positions and phases of respiration. Acceptable, that is, physiological murmurs are in the main pulmonary in location and systolic in time. They vary with both body position and respiratory phase, being loudest in the supine position and in full expiration, and becoming faint or disappearing in the upright position or at full inspiration. Other murmurs that may be passed as normal are those produced in the lungs by the heart beat itself, that is, the sound of currents of air and not of blood, and secondly, trivial or at most slight systolic murmurs at apex, aortic area, or over the lower sternum which tend to disappear like the louder pulmonary systolic murmurs with changing body position or respiratory phase. But it is important to remember that, at least in adults

who are not ill with anemia or acute infections, apical and aortic systolic murmurs are usually indicative of pathological conditions in heart or aorta.

Finally, I would say a few words about *neurocirculatory asthenia* even though it has been moved in the Army and Selective Service listings from under the cardiovascular heading to that of neuropsychiatry where it may not really belong either. It can be made to fit everywhere for it is evidently a condition that can follow or attend all sorts of diseases. It is, I believe, best defined as I gave it in a recent leaflet of the American Heart Association, one of their so-called Modern Concepts of Cardiovascular Disease (the August number): "Neurocirculatory asthenia is a condition of ill health characterized by a group of symptoms consisting of dyspnea (often with sighing respiration also), palpitation, precordial pain (more often an ache), exhaustion, dizziness, nervousness, and sometimes tremor, sweating, headache, and syncope, aggravated by effort or excitement, and attending or following infection or physical or nervous strain, especially in 'hypersensitive' individuals, who in extreme cases may show the condition more or less constantly with little or no provocation." In other words it is not a specific disease itself as far as we know, although it may in some cases seem to stand more or less alone. Its pathogenesis is unknown. As good a suggestion as any is that it is a disorder of the vegetative nervous system precipitated by a variety of factors which in peace time or in training camps in war time are predominantly the anxiety psychoneurosis and infectious disease, but which in the stress and strain of combat can include physical and nervous exhaustion, then being rather a fatigue syndrome. Naturally, therefore, both in peace and in war the psychoneurotic looms largest among the subjects with the condition and the syndrome has therefore sometimes been labelled as "anxiety neurosis." I believe, however, that it is best to consider it rather as a result or accompaniment of an anxiety neurosis, since I have seen patients neurotically anxious about their hearts without these characteristic symptoms and I have seen other patients with these symptoms who had never been nor were at the time, so far as I could tell, afflicted with any psychoneurosis. Yet despite its varied etiological background neurocirculatory asthenia is a condition of ill health that exists and as yet in my opinion cannot be designated by any better term. Undoubtedly it has been labeled as but a part of its exciting factor in the majority of cases when it is relatively mild and its exciting factor prominent, as in the case of some acute infectious disease, fatigue state, or psychoneurosis. But sometimes the exciting factor is not so evident or the syndrome itself is of considerable degree, and then it stands as the main diagnosis. Hence it has not loomed large among the causes for rejection from the armed services even though it is a common and sometimes marked finding in many of the cases turned down, and rightly so, for a psychoneurosis.

Among the men whom Drs. Cobb, Graybiel, Cohen, Chapman, and I have already seen and studied in army hospitals with the label neurocirculatory asthenia, a psychoneurotic state, chiefly an anxiety neurosis, stands pre-

eminent and was present in almost every case, and nearly always was quite marked before enlistment. These men are obviously constitutionally inferior and should never have been admitted to the Army. I really doubt whether we are justified in passing any at all who have the condition under the lesser strains of peace time despite the recommendation in MR 1 to 9 that we may accept registrants with neurocirculatory asthenia if it is very mild in degree. We did recently add the "very," but it is more and more my belief that if the condition can be recognized at all in peace time and is not provoked by some correctible factor, the registrant should be rejected, for these cases become awful headaches for the doctors in service. One should not admit them with the idea that training will help them to outgrow their state of ill health.

It's another matter when neurocirculatory asthenia appears for the first time after enlistment. The more severe the strain needed to bring out the condition, the less need be our concern about it. Rest for a few days or a few weeks should relieve the symptoms and an attempt should be made to avoid soon subjecting that person again to such a severe strain. But when preliminary or only moderate drilling induces neurocirculatory asthenia and a careful training program does not quickly alleviate it, either the soldier should be discharged if his limitations are great or given less strenuous or more suitable tasks (if possible) if his limitations are only slight to moderate. We should be able to exclude enough of these men at the source so that we shall not be in the predicament that faced the British after the last war when they were saddled with 44,000 cases of "effort syndrome" who became pensioners, or that faced DaCosta who wrote as follows: "The treatment is never a short one; and the question arises, would it not be better for the government at once to discharge these heart cases? I think not. The very worst ones, those which after some months of treatment show no decided improvement, had better be discharged; so had those which happen in the very young, or in soldiers in whom some decided complicating ailment exists, which is likely to prevent the cardiac malady from entirely leaving; though even some of these can be kept as fit for guard duty, for service in hospitals, or in convalescent camps. But all other cases should be kept for treatment; and then either, if fit, sent back to their regiments, or passed into such organizations as the Veteran Reserve battalions during the late war,* which were intended to do provost duty, to serve in fortified places, in fact, to do everything except active service in the field. And from these organizations again, should the war prove a protracted one, the cases that have thoroughly recovered may be sent to rejoin their former regiments. To act otherwise, to discharge the large number of cases of functional disorder of the heart, which must exist in every army during war, would, I believe, deplete it as much as an engagement, and have on many a soldier, seeing the ease with which a discharge can be obtained, a demoralizing effect. As for the time required before the disposition of a case is made, this depends much on judgment in individual

* Our Civil War.

instances, and while, until I understood the malady, I retained a number of patients a long period in the hospital, later in the war a short time sufficed to make a proper disposition of them."

To avoid DaCosta's dilemma and that which faced the British Army, and ourselves too for that matter, during the first World War, we must attempt to weed out of the registrants those individuals who are obviously afflicted with the condition in peacetime. Even if we are able to do that we shall still have enough cases among the soldiers of tougher fiber when the fighting gets rough enough, but we should expect to avoid the great majority of the military neurocirculatory asthenic cripples of former days. Since in peacetime the characteristic neurocirculatory asthenia patient is a psychoneurotic with an anxiety neurosis, it is to the psychiatric part of the induction examination that we should naturally turn for help. I believe that such examination has already borne rich fruit for we find that relatively few very definite cases of neurocirculatory asthenia actually have been hospitalized through the U. S. A. as yet. Let us hope that this may be the answer, and, if it is, stress still more the importance of the psychiatrist with his feet on the ground, in any examining group.

Exercise tests such as Lewis suggests may be useful too, but they are open to a number of objections: first, the difficulty of giving each man an appropriate exercise for his degree of physical training; second, the uncertainty of the results on occasion, as, for instance when the registrant has caroused the night before celebrating his departure for the Army or for other reason; and third, though less important, because of the extra trouble that such a test entails. Certainly, when one is in doubt, however, recourse should be had to some simple exercise such as stair climbing, or the chair mounting or two-step test.

My time is up, but I hope that I may have helped to clarify in your minds our chief cardiac problems in war time in this year 1942 even if I have been unable to give you all the answers.

MYXEDEMA HEART: A PATHOLOGICAL AND THERAPEUTIC STUDY *

By JOHN S. LA DUE, M.D., *New Orleans, Louisiana*

THIS report presents the autopsy findings in a patient dying of heart failure due to myxedema and points out the similarity of her myocardial lesions to those found in the beriberi heart. The case history of another patient with myxedema heart treated with thiamin and vitamin B complex and then with thyroid extract is reviewed.

The clinical syndrome of heart failure sometimes associated with hypothyroidism (myxedema heart) was first described by Zondek [1] in 1918. It was later recognized in this country by Fahr [2] and has since been discussed by many investigators.[3] Hallock [4] showed that the cardiac output of the myxedema heart was low and that it was increased by the administration of thyroid extract. Descriptions of the pathological changes in the heart muscle are few and controversial.

Schultz [5] described the pathological findings in a 12 year old girl with congenital athyrosis who died from myxedema heart failure. The heart was generally dilated, the muscle pale, and a normal amount of pericardial fluid was present. The cardiac muscle cells were filled with hydropic vacuoles and there were fragmentation and branching of individual fibers with loss of striations. These vacuoles did not stain for fat or mucus. Mucus was found in the wall of the aorta and in the perineurium of some of the nerves.

Behr and Mülder [6] published an autopsy report of a patient with myxedema heart with severe congestive failure who died after five days of intensive thyroid therapy. The heart was generally dilated, weighing 335 grams, the muscle pale with rather extensive fibrosis and narrowing of the coronary arteries. Histologically, besides the fibrosis, the muscle cells stained irregularly. Many fibers were swollen, their nuclei pyknotic and the striations absent. In many cells the sarcoplasm was replaced by hydropic vacuoles. These changes were most pronounced in sections taken from the subendocardium, although they were found diffusely. The vacuoles failed to stain for fat, mucus or glycogen. Webster and Cooke [7] noted similar involvement in the myocardium of rabbits 185 days after complete removal of thyroid tissue. Brooks and Larkin [8] were unable to detect such changes 40 days after thyroidectomy.

Elsewhere in the literature [9] reports are inconclusive because autopsies were performed long after thyroid therapy was begun or because microscopic studies were not made and unusual myocardial involvement was hence not noted.

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Lufkin [10] has briefly reported the pathological findings in a woman dying of hypothyroidism associated with severe heart failure. A more complete review of the clinical and pathological picture exhibited by this patient is herewith presented with his consent.

Case Report

The patient, a 52 year old housewife who entered the Minneapolis General Hospital on November 29, 1936, had had intermittent dyspnea, orthopnea and edema of the lower extremities for two years, with increasing distress since June, 1936. An informant stated that since 1929 the patient manifested increasing weakness and fatigue and had come to do her household work with maddening slowness. Relatives

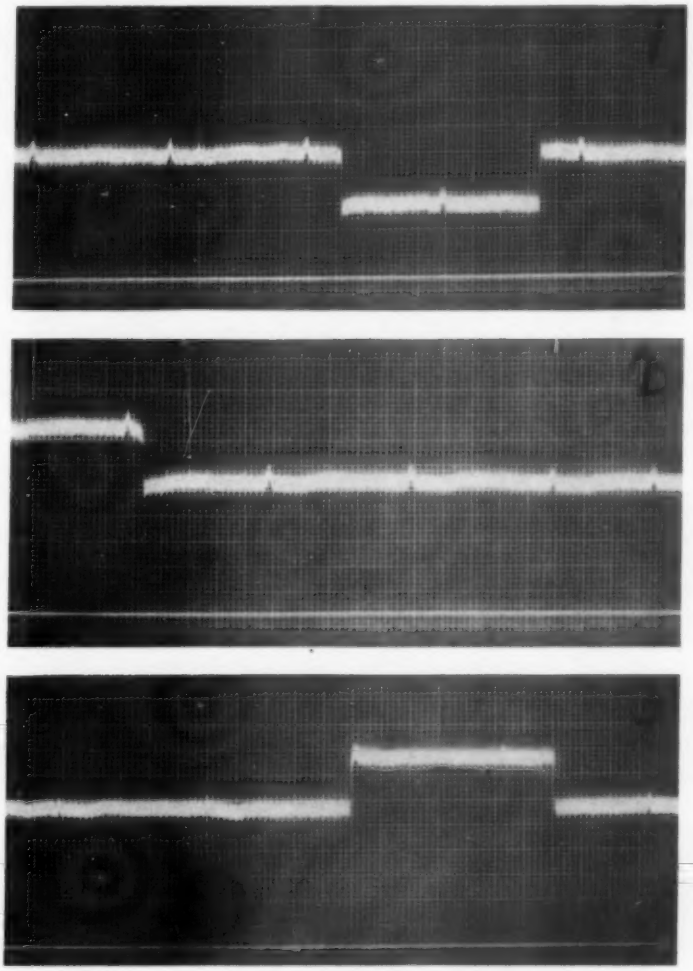

Fig. 1. Electrocardiogram taken six hours before death showing an extremely low potential, at its highest only 0.2 millivolts. T_1 is isoelectric, T_2 and T_3 are negative. These changes are consistent with myxedema heart.

said that a marked slowing of her mental processes, together with extensive loss of memory, dated from 1933. About a year later other changes were noted. She complained bitterly of chilliness, her voice grew increasingly hoarse, and despite loss of appetite she gained weight. Weakness progressed markedly, her complexion became pale and she sat about apathetically, refusing to move unless it was absolutely necessary. Various physicians treated her for heart failure, kidney trouble and anemia. Liver extract and digitalis were taken without improvement. Physical examination revealed a moderately obese patient who was unable to answer questions. She was markedly cyanotic, propped up in bed and gasping for breath. Her hair was coarse and her eyebrows scanty; the face and eyelids were swollen and the lid slits narrowed. The skin was dry, thick and pale yellow in color. The neck veins were distended, but the thyroid was not palpable. There was dullness over both lung bases and crepitant râles were heard. The heart seemed enlarged to percussion, the rhythm was regular, the tones were faint, and no murmurs were heard. The blood pressure was 115 mm. Hg systolic and 70 mm. diastolic. The abdomen was obese, with shifting dullness in both flanks, and the liver was felt 10 cm. below the costal margin in the right midclavicular line. There was massive pitting edema of both lower extremities. The clinical diagnosis was hypothyroidism with myxedema heart in congestive failure.

The hemoglobin was 47 per cent, the specific gravity of the urine 1.018 with a faint trace of albumin and 6 to 8 white blood cells per high power field. The electrocardiogram (see figure 1) showed an extremely low potential, at its highest only 0.2 millivolts. T_1 was isoelectric, T_2 and T_3 were negative.

The patient lived just seven hours, apparently dying of congestive heart failure. Autopsy was performed nine hours after death.

The body was that of a well developed, obese woman weighing approximately 200 pounds. Rigor and hypostasis were present. There was massive edema of the legs, thighs and back, less marked over the dorsal surface of the hands and over the eyelids. The hair was thin, coarse and dry and the skin slightly yellowed.

About 1000 c.c. of straw colored fluid filled the peritoneal cavity; approximately 800 c.c. of amber fluid were found in the right pleural cavity and 400 c.c. in the left. The pericardial sac contained 30 c.c. of clear, watery fluid.

The heart was globular, weighed 400 grams, and measured 14.5 cm. at its greatest transverse diameter (figure 2). Both auricles and ventricles were dilated and their myocardial surfaces smooth and glistening. The valves showed no pathological changes. The left ventricle was moderately hypertrophied and dilated, the right slightly thicker than normal but greatly dilated. The heart muscle was pale red throughout and possibly a little soft, but no fibrosis or other focal lesions could be found when the muscle was sectioned. The coronary orifices were patent and of normal dimensions. The descending branch of the left coronary artery showed slight diffuse thickening without appreciable lumen alteration and two centimeters from its point of origin it divided into right and left rami. Here there was an atheromatous nodule which abruptly reduced the caliber of the left vessel to one-half. This nodule also extended 0.5 cm. into the right ramus, reducing its lumen to one-third. The other coronary vessels were free of significant changes.

The right lung weighed 450 grams, the left 500 grams. Crepitation was diminished throughout both lungs and a frothy fluid oozed from their cut surfaces.

The liver weighed 1300 grams and its lower margin extended 10 cm. below the costal margin in the right midclavicular line. The cut surfaces were slightly yellow, but scattered throughout there was evidence of chronic passive congestion with enlargement and reddish discoloration of the centers of the liver lobules. The gall-bladder contained two green calculi and its wall was somewhat thickened.

The stomach was filled with 300 to 400 c.c. of dark hemorrhagic fluid and blood clots. Near the antrum several ulcers, some superficial and others extending into the

submucosa, were noted. A few of these ulcers were surrounded by elevated margins; none was more than 3 to 4 mm. in diameter. The jejunum and ileum were filled with hemorrhagic material but the mucosa of the entire intestine was intact.

The pancreas, adrenals, genitourinary tract, uterus, tubes and ovaries appeared normal.

The dorsal aorta contained numerous small, soft, yellowish plaques.

The thyroid weighed only seven grams, was fibrous and contained no visible colloid.

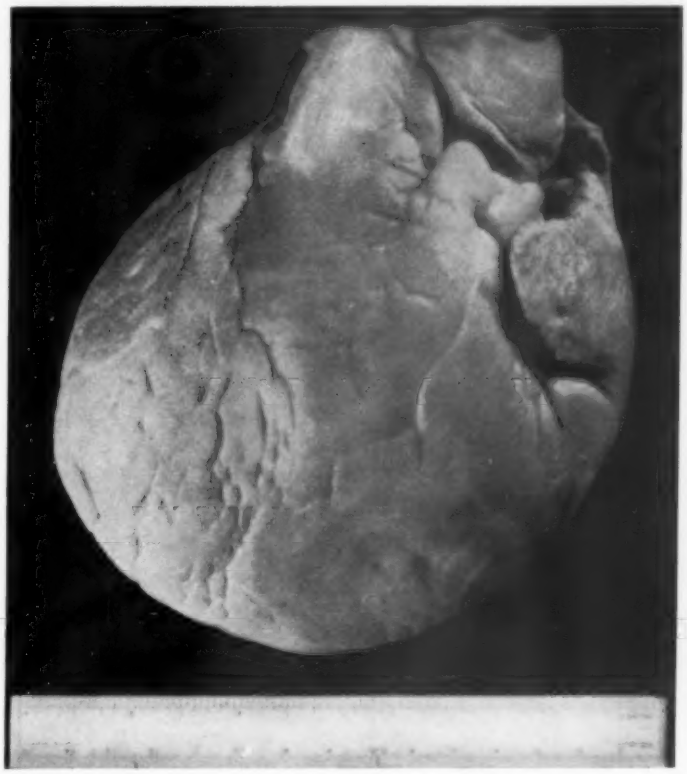

FIG. 2. Globular shaped heart of the patient dying with myxedema heart. Its transverse diameter is 14.5 cm. and it is generally dilated.

Microscopic examination revealed that the thyroid gland was markedly atrophied; many acini were replaced by fibrous tissue and only a few acini contained colloid. There were small areas of polymorphonuclear infiltration about the bronchi of the lungs and many alveoli were filled with red blood cells; heart failure cells were prominent. The centers of the liver lobules were packed with blood and surrounded by atrophied liver cells. Sections of the gastric ulcers showed loss of mucosa with edema and leukocytic infiltration about their edges and to a lesser extent in their bases.

Sections of the heart muscle just beneath the endocardium showed striking changes. In many places the sarcoplasm of the myofibrils was completely replaced by hydropic vacuoles. Elsewhere there were branching and loss of striation of individual fibers. Some of the cells were pale, others were deeply stained, small, and had

pyknotic nuclei. Stains of the vacuoles were negative for fat, mucus and glycogen, indicating a true hydroscopic swelling similar to that noted in the edematous tissues of patients with myxedema. These changes were present but much less pronounced in other sections of the myocardium.

These findings are the same as those described by Schultz,[5] Behr and Mülder [6] and Webster and Cooke [7] and were thought to be specific by these investigators. Ceelen [11] has suggested that they are the result of changes (sclerosis) in the coronary vessels accentuated by the disturbance of lipoid metabolism. Higgins [9] also subscribes to this point of view, but states that early involvement of the heart may consist of "mucin-like infiltration of the muscle fibers which can be overcome by the judicious use of thyroid extract." However, the studies of Schultz,[5] Behr and Mülder [6] and of the case reported here indicate that the "mucin-like infiltration" is not mucus, fat or glycogen but hydroscopic edema. Arteriosclerotic damage of the myocardium was conspicuously lacking in Shultz's case, in the case described here and in many of the experimental studies. It is, therefore, probable that fibrosis of the heart muscle is not a specific result of myxedema.

In searching for evidence to prove or disprove the specificity in myxedema of such changes in the heart muscle as vacuolization, loss of striation, branching, inequality of staining and the pyknotic nuclei of muscle fibers, we tried to detect these processes in other types of myocardial disease. Dr. Lufkin [12] examined a series of hearts in elderly patients dying of heart failure and from other causes and discovered strikingly similar changes in the His bundles. In examining a series of dog hearts for other changes, I found many areas of involvement not unlike those seen in our myxedema heart. These animals had been unable to retain their feedings for as long as 21 days.

Wenckebach [13] has stated that hydropic swelling of the myofibrils, loss of striation and intercellular edema are characteristic, if not specific, for beriberi heart. Weiss and Wilkins [14] also detected these changes in 21 patients with polyneuritis and pellagra with or without cardiovascular dysfunctions. The myocardial fibers and conductive tissue of this group showed various degrees of hydropic swelling. Similar changes were seen to a lesser degree in a few of the hearts of 36 controls. These investigators concluded that these histological alterations were not indicative or specific in beriberi heart or in the hearts of patients suffering from polyneuritis and pellagra. Figure 3 illustrates the similarity of the histological changes in myxedema heart (photomicrograph from sections of the heart of the patient reported here) and beriberi heart (reproduced from Weiss and Wilkins). Both exhibit hydropic vacuolization of muscle fibers, branching and loss of striation.

Some time after the first report of this case, another patient with myxedema and myxedema heart in mild failure was admitted to the Minneapolis General Hospital and it seemed worthwhile to test the therapeutic properties of thiamin and the vitamin B complex on this patient. After a brief control period during which necessary laboratory studies were made, the patient was

given intensive vitamin B therapy for 33 days and the laboratory studies were then repeated. Thyroid extract was then administered and the laboratory studies again repeated. Findings are given in the case report.

Case Report

The patient, a 43 year old housewife, entered the hospital on the dermatology service on December 7, 1939, asking to be treated for small yellowish nodules which had

Fig. 3. (Above) Photomicrograph of myocardium of the heart shown in figure 2. Note replacement of sarcoplasm of the myofibrils by vacuolization. There is loss of striation and branching of some of the individual muscle fibers.

(Below) Photomicrograph from Weiss and Wilkins [14] of a section of the myocardium of a beriberi heart. Note similarity to above.

appeared on her hands, feet and body during the preceding 18 months. She had also noticed increasing weakness, malaise, dry skin, hoarseness, cold sensitivity and impairment of hearing. The first change in her skin had been the appearance of a yellowish discoloration on the palms of both hands. Within six months small, painless, lemon-colored lumps had formed at the bases of the fingers; soon they were noted on the feet and later on the trunk. Her complexion grew muddy and yellow, her skin dry, coarsened and later wrinkled. Her hair had always been coarse and dry and her eyebrows scant but these faults were accentuated after the onset of the present illness.

Although these objective changes occupied most of her attention, she stated that she felt that she was becoming "old." She had difficulty in recalling recent events; conversation required great attention and quickly tired her. She was unable to concentrate or to formulate ideas and said that her speech was impaired because of a "thick tongue." Her voice became coarse and words had to be formed slowly. Her hearing, which had been excellent, became poor. One of the most distressing symptoms was the acute discomfort produced by moderate exposure to cold. Weakness was progressive, so that she was finally unable to do her housework, and she found herself irritable and short with her children. The menstrual cycle, previously normal, was irregular and the flow excessive.

A week before coming to the hospital she had noticed increasing swelling of the ankles, mild dyspnea on exertion and palpitation. There was no precordial pain.

TABLE I

Summary of Laboratory Data for Patient 2

Determinations	Control Period (Dec. 7–Dec. 21)	After Thiamin (Dec. 21–Jan. 23)	After Thyroid (Jan. 23–Feb. 26)
Basal metabolic rate	−28% and −24%	−35% and −37%	−8% and plus 10%
Roentgenogram Ml. Heart Mr.	9.0 cm. 5.9 cm.	8.8 cm. 5.8 cm.	6.8 cm. 4.8 cm.
Electrocardiogram	Typical for myxedema heart	Unchanged	Normal
Cholesterol	540 mg. %	870 mg. %	268.4 mg. %
Hemoglobin	50%	55%	62%
Red cell count	2,530,000	2,920,000	3,270,000

The patient was a well-nourished, but not obese woman, who looked older than her 43 years. Her voice was hoarse and she spoke in a slow, drawling manner, pausing for several moments before answering questions. She did not seem dull, but reacted very slowly.

The face was wrinkled but expressionless, the complexion muddy yellow. The hair was coarse and brittle but fairly abundant; the eyebrows looked moth-eaten. The lids of the eyes were slightly edematous and a yellow nodule 1 to 2 mm. in diameter was seen on the right upper eyelid. The conjunctivae were pale and in the right there were four fatty nodules. The patient was edentulous and the mucosa of the mouth had a yellowish cast. The skin was dry and flaky. Both palms were a pale yellow color which was intensified in the skin creases. Yellow nodules 1 to 4 mm. in diameter were scattered diffusely over both palms and about the joints of the fingers on the backs of the hands. The nodules were freely movable and not tender. Similar lesions, 1 to 6 mm. in size were present on both knees, on the skin covering the Achilles' tendon, and on the dorsal and plantar surfaces of the feet.

The lungs were resonant throughout and no râles were heard. The heart was enlarged to percussion, ml. being 9.0 cm. and mr. 6 cm. The heart sounds were distant and faint, the rhythm regular, and the rate 86. No murmurs were heard, the aortic second sound was equal to the pulmonic second, and the blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. The abdomen was soft and there were no

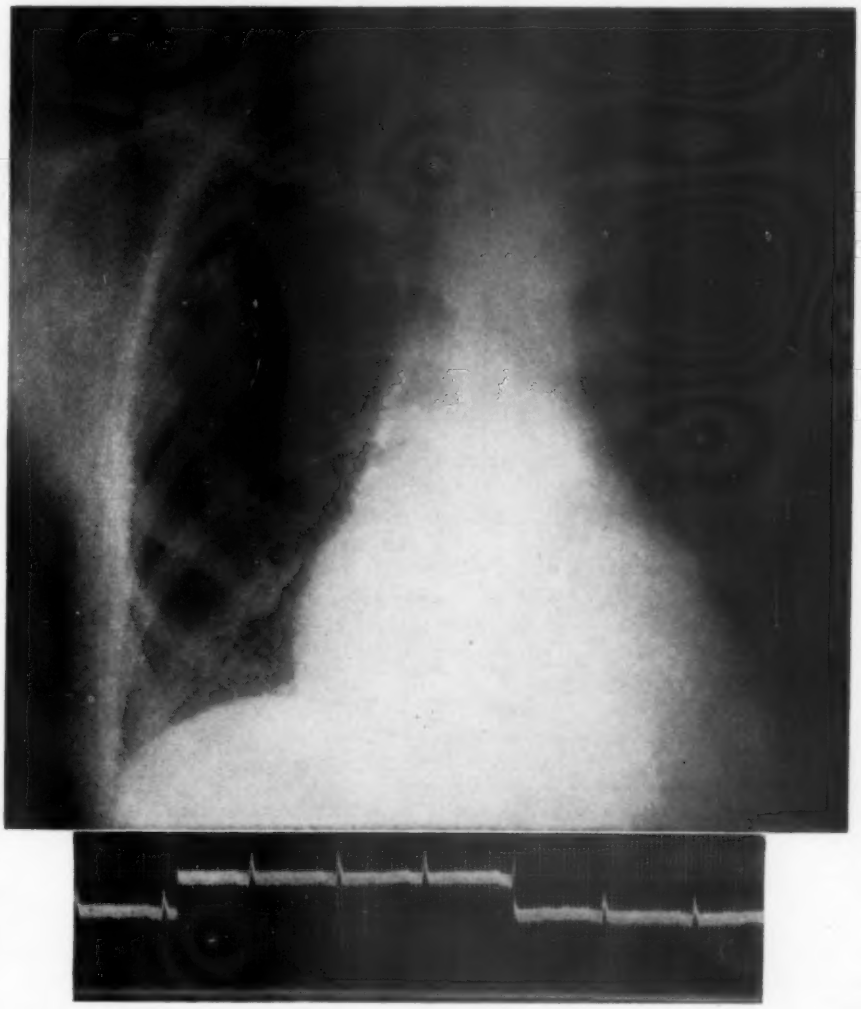

FIG. 4. Teleoroentgenogram and electrocardiogram of Patient 2, illustrating generally dilated heart and electrocardiogram typical of the myxedema heart, before any treatment was instituted.

palpable masses or viscera. The extremities were symmetrical, with a 2 to 3 pitting edema of both ankles. Reflexes were sluggish but equal. Both the knee and the ankle jerks had a normally active contraction but relaxation was unusually slow.

Most of the important laboratory findings are summarized in table 1. The serum proteins were within normal limits, with a globulin of 1.7 per cent, an albumin of 5.5 per cent and a fibrinogen of .16 per cent. On December 22, 1939, the vitamin C level

was 0.2 mg. per cent and before discharge it had risen to 0.8 mg. per cent. The phenolsulphonphthalein elimination was essentially normal. A cholesterol tolerance test on December 21 gave the following: Fasting level 565, 2 hours 800 mg. per cent, 4 hours 571 mg. per cent, 8 hours 835 mg. per cent, 24 hours 835 mg. per cent. A glucose tolerance test on December 12 showed a fasting level of 85 mg., a peak of 155 mg. at one hour and a level of 120 mg. at the end of three hours. A biopsy of the skin from the right foot showed a diffuse edema of the subepithelial connective tissue. Numerous lipoid-containing cells were scattered throughout the section and an edema and a cellular exudate were seen about the sweat glands. A microscopic section of one of the nodules showed fibrosis with cholesterin clefts within the fibrous areas. The basal metabolic rates, electrocardiograms and roentgenograms are included in the discussion of the course of the disease and summarized in table 1. Course: The patient was not seen by the medical service until the seventh hospital day. At this time there was no edema and the venous pressure was 8 cm. of sodium citrate (normal). No trace of congestive failure could be found. On December 8 the basal metabolic rate was — 28 per cent and on December 14 it was — 24 per cent. On December 16 a six-foot roentgenogram of the heart was made and these measurements reported: transverse thoracic 23.7 cm.; ml. 9.0 cm.; mr. 5.9 cm.; total 14.9 cm. and the arch 3.2 cm. Fluoroscopically, the pulsations of the heart were of decreased amplitude. There was no evidence of pulmonary congestion. An electrocardiogram taken the same day showed a low potential in all leads, isoelectric T_1, extremely low T_2, T_3 and an M shaped QRS_3 (figure 4).

In view of the clinical and laboratory findings, diagnoses of myxedema with myxedema heart and generalized xanthomatosis were made. No medications, except ferrous sulfate gr. iii twice a day, were given until the patient was transferred to the medical service. In accordance with our plan, after a short control period 50 mg. of thiamin chloride were administered parenterally each day. This drug was given for 33 days and supplemented for the last 15 days by brewers' yeast and cod liver oil tablets (grs. x four times a day). During this period, five electrocardiograms and two six-foot roentgenograms of the heart were taken. The electrocardiogram remained essentially unchanged and the cardiac measurements at the end of this phase of therapy were: ml. 8.8 cm., mr. 5.9 cm., total 14.5 cm.; arch 2.9 cm. (figure 2). After 20 days of thiamin therapy the basal metabolic rate was — 36 per cent (figure 5).

Since there was no apparent improvement after 33 days of intensive vitamin therapy, thyroid extract was begun on January 23, 1940, the forty-eighth hospital day. The drug was first given in doses of one-half grain twice daily and the dosage was increased gradually until on February 3 (the fifty-ninth hospital day) one grain was taken three times a day.

On January 30, eight days after starting thyroid extract, T-waves had appeared in all three leads of the electrocardiogram and the QRS voltage was slightly increased. On February 16, after 25 days of thyroid medication, the electrocardiogram was essentially normal with T-waves 3 to 4 mm. in height and QRS deflections of 7 to 12 mm. On the same day, the transverse thoracic diameter was 26.4 cm., the ml. 6.8 cm.; the mr. 4.8 cm.; total 11.6 cm.; arch 2.8 cm. (figure 6). The basal metabolic rate was — 8 per cent on February 9 and plus 10 per cent on February 26, the day before discharge.

Before the patient left the hospital there had been a marked amelioration of all the symptoms and signs which were previously so distressing. This change dated from the day thyroid medication was begun and all improvement prior to this time was minimal and could be ascribed to the rest and care of hospitalization. Several days after thyroid extract was begun the patient noted a sense of well being, conversed at length, and stated that her hearing had improved. Her skin gradually

became moist and soft and her hair somewhat less dry and brittle. The pitch of her voice was raised and all hoarseness and halting manner of speech disappeared. Before she left the hospital much of the yellow color of her skin had faded, although the xanthomatous nodules remained unchanged.

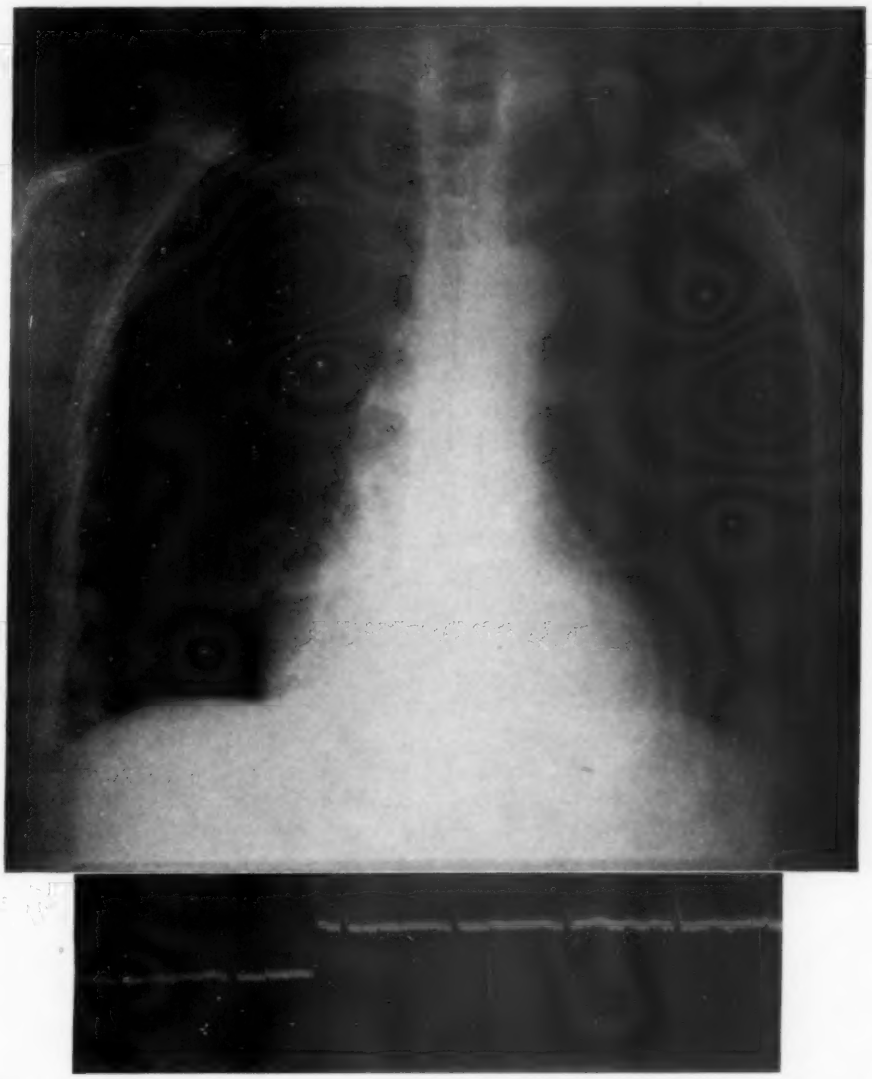

FIG. 5. Teleoroentgenogram and electrocardiogram of the same patient after 33 days of intensive vitamin B therapy (thiamin and B complex). There is no appreciable change; the slight increase in voltage of the electrocardiogram is due to improper standardization.

She was seen on several occasions in the out-patient department but had no complaints and the xanthomata of the skin appeared smaller. Several basal metabolic measurements were made, with values ranging from —8 per cent to +10 per cent. Thyroid extract was taken in doses of one grain three times daily. The glucose

tolerance was repeated, the fasting level was 80 mg. per cent, the peak 150 mg. per cent, and at the end of two hours the value had fallen to 85 mg. per cent. Ferrous sulfate was continued, and on April 6, 1940, the hemoglobin was 96 per cent and the red blood cells 4,300,000. The cholesterol never went above 240 mg. per cent and the cholesterol tolerance test was not repeated.

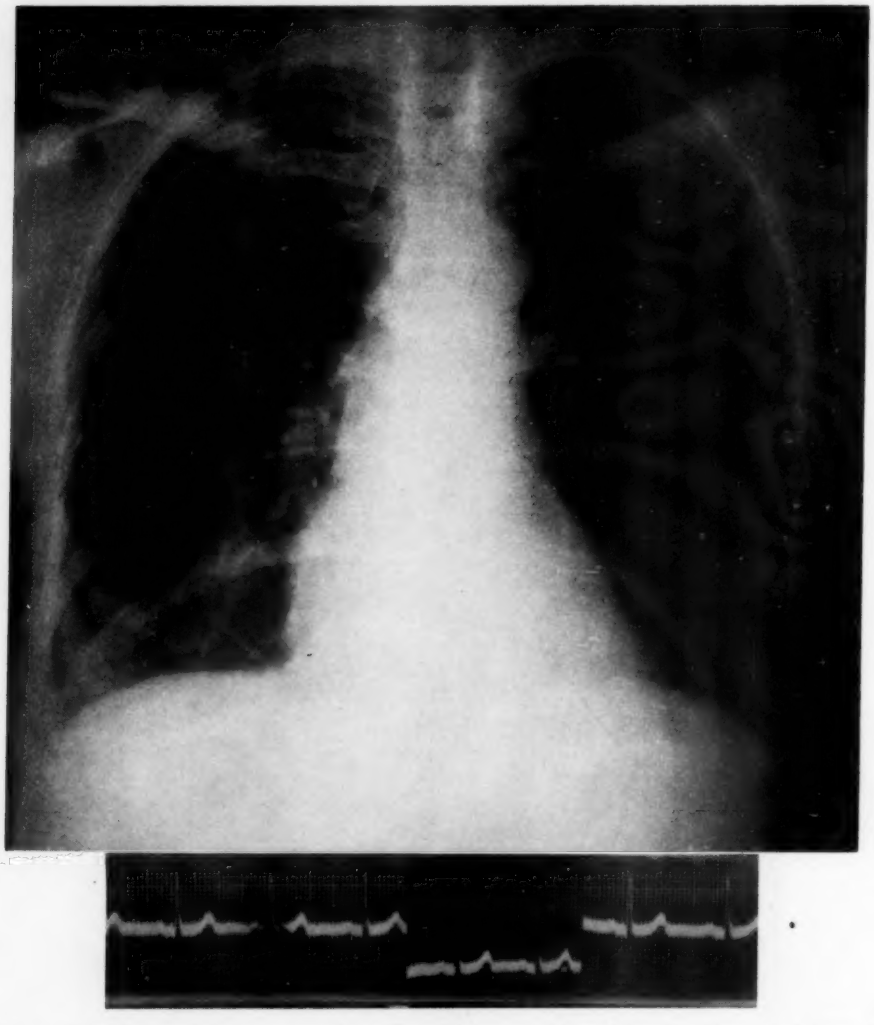

FIG. 6. Teleoroentgenogram and electrocardiogram of Patient 2. Note shrinkage in transverse diameter of the heart and prompt return of electrocardiogram to normal after 25 days of thyroid medication.

DISCUSSION

Changes in the muscle fibrils of the myxedema heart such as vacuolization, loss of striation, branching, pyknotic nuclei and irregularity of the staining properties may be found in other conditions. Wenckebach [18] and

Weiss and Wilkins [14] found these changes in beriberi heart, but the latter workers, as well as Lufkin, demonstrated identical processes in the hearts of patients dying other than cardiac deaths. The writer noted a similar picture in the hearts of dogs starved seven to 21 days. There is nothing to indicate why the same pathological picture should occur in widely different conditions, but it is significant that it is the chief pathological abnormality of the myxedema heart.

In myxedema, characteristic electrocardiographic disturbances are seen, but variable tracings are obtained from the patients with beri-beri heart and non-cardiac conditions. Either identical pathological processes fail to produce typical electrocardiographic patterns or the metabolic disturbance is primarily responsible for the electrocardiogram in myxedema.

Thiamin and vitamin B concentrate, although extremely effective in the treatment of beriberi heart, completely fail to improve the myxedema heart which responds promptly to thyroid medication. Perhaps in the future some physiologic relation between the vitamins and thyroxin may be discovered, but at present the results of such investigations are controversial.

Hundhausen [15] demonstrated that B_1 decreases thyrotropic and gonadotropic hormone secretion in the rat. Elmer [16] showed that excessive vitamin B_1 did not diminish the action of thyroid extract. Mitchell [17] proved excessive doses of vitamin B to have no effect on basal metabolism. Drill [18] found that large doses both of B_1 and of B_2 given to hyperthyroid rats resulted in an increase in weight. B_1 alone did not. Löhr [19] stated that vitamin B_1 deficiency symptoms and the symptoms of hyperthyroidism are strengthened by each other. Means [20] and Frazier and Raydin [21] believe that vitamin B_1 should be given preoperatively to patients with hyperthyroidism.

Conclusions

1. Hydropic vacuolization, loss of striation, branching, pyknotic nuclei and irregularity in staining properties of the muscle fibrils are seen in myxedema heart but are not specific for this entity.

2. Thiamin and vitamin B complex are ineffective therapeutic agents for myxedema heart.

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ABDOMINAL PAIN IN PULMONARY THROMBOSIS*

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In the past 16 years the antemortem diagnosis of pulmonary thrombosis has been made in 53 subjects disclosing this lesion at necropsy in the Wisconsin General Hospital. The criteria for this clinical diagnosis are familiar but frequently minimized. An analysis of these data is, therefore, undertaken before recounting the unusual occurrence of abdominal pain in pulmonary thrombosis.

The incidence of pulmonary thrombosis was much more frequent in men than in women (41 men to 12 women, a ratio of 3.4:1). The age distribution follows:

Age	Number	Per Cent
21–30	4	7.5
31–40	8	15.
41–50	11	20.9
51–60	16	30.1
61–70	7	13.2
71–80	6	11.3
–82	1	1.7

Although the dispersion is quite wide, one-half of the incidence appeared in patients between 41 and 60 years of age. In the four patients dying in the third decade (at 24, 25, 26 and 28 years respectively), the rheumatic state was the constant etiological background. In two of these, rheumatic endocarditis was the pathological diagnosis; in the third, adhesive pericarditis (rheumatic); in the fourth, *Streptococcus viridans* endocarditis lenta on a rheumatic background.

Cardiovascular lesions dominated the clinical and pathological diagnosis:

Diagnosis	Number	Per Cent
Arteriosclerotic heart disease	30	56.6
Rheumatic heart disease	12	22.6
Syphilitic heart disease	2	3.7
Streptococcus viridans endocarditis lenta	2	3.7
Adhesive pericarditis	1	1.7
Vascular nephritis	1	1.7

The remaining diagnoses included bronchiogenic carcinoma (2), carcinoma of the uterus (1), prostatic hypertrophy (1), and multiple abscesses of the liver (1). Included in the arteriosclerotic group were four subjects with coronary occlusion, of whom two had developed aneurysm of the left ventricle. One patient with syphilitic aortitis had an aneurysm of the aortic arch. Thirteen of the total cardiovascular group had auricular fibrillation. The functional capacity of these patients was established in this distribution:

Functional Capacity	Number	Per Cent
Grade I	6	11.3
Grade II	1	1.7
Grade III	4	7.5
Grade IV	42	79.2

* Received for publication March 26, 1942.

The overwhelming preponderance of a sharp limitation of the circulatory reserve of this group of patients fixes their general type and handicap. It is significant, however, that pulmonary thrombosis can occur in the absence of any myocardial insufficiency (6 or 11.3 per cent).

The clinical course of pulmonary thrombosis commonly follows a regular sequence. In this series the onset of symptoms was precipitous in 23 (43.3 per cent) and gradual in 24 (45.2 per cent). In six patients (11.3 per cent) the history did not justify a decision in this detail. The most frequently occurring symptoms are listed as follows:

Symptoms	Number	Per Cent
Dyspnea	48	90.5
Hemoptysis	33	62.2
Apprehension	16	30.1
Cough	13	24.5
Pain	13	24.5
Symptoms of shock	11	20.9
Oppression	5	9.4

The strikingly high incidence of dyspnea should be remarked. Over 90 per cent of these patients experienced dyspnea with the inception of pulmonary thrombosis. Apprehension was noted in 30 per cent, and there were many grades of concern to actual fear of death in several individuals. At varying periods after the onset of symptoms hemoptysis occurred in 62.2 per cent. The absence of blood-spitting does not exclude this diagnosis. The lower percentage listed as coughing depends upon the inclusion of only those patients who developed coughing after the initiation of the pulmonary accident. The pain of pulmonary occlusion appeared in 24.5 per cent, early in its course. Deep seated in the thorax it may be so severe as to be mistaken for coronary occlusion. The pain was independent of pleural involvement and greatly augmented the apprehension. A sense of intrathoracic oppression may attend and accentuate the pain or may occur without relation to it. Symptoms of shock were noted in 20.9 per cent.

The physical findings of importance may be grouped thus:

Signs	Number	Per Cent
Râles	36	67.9
Cyanosis	32	60.3
Jaundice	20	37.7
Pleural friction	17	32.
Altered breath sounds	14	26.4
Dullness	11	20.9
Cheyne-Stokes respiration	9	16.9
Coma	4	7.5

Particularly significant among the physical signs of pulmonary thrombosis were suddenly developing cyanosis (60.3 per cent) and localized small and medium moist râles (67.9 per cent). At the site of these directional râles there later appeared evidences of altered air content and sound conduction (20.9 and 26.4 per cent, respectively). The breath sounds were usually reduced, but occasionally they approached a bronchial quality. Obviously the size and accessibility of the area supplied by the involved pul-

monary artery will determine these signs. The pleural friction rub, heard in 37.7 per cent, is frequently a clinching diagnostic clue, especially if there be no reason to suspect a pneumonic complication. Particular attention should be paid to the jaundice of pulmonary thrombosis. Rich and Resnik [1] have demonstrated the responsibility of a marginal hepatic functional integrity for this occurrence. With the extravasation of blood into the pulmonary tissue relatively rich in reticulo-endothelium there is an opportunity for the increased formation of bile pigment. Coincident with the accident of pulmonary occlusion the hepatic parenchyma, already handicapped by passive congestion and central necrosis (Keefer and Resnik [2]) as a rule, is further embarrassed by the anoxia attendant upon the circulatory depression of the accident. Hence, a functional intrahepatic obstructive jaundice occurs (37.7 per cent). The icterus index was not regularly determined, but where available it usually ranged from 15 to 30. Two instances of 100 were recorded. The occurrence of coma and Cheyne-Stokes' respiration may be related to the vascular status and the general debility of a considerable number of these patients.

The survival period of the group ranged from two minutes to 142 days. The data have been grouped as follows:

Survived	Number	Per Cent
Less than 1 hour	3	5.6
1 to 12 hours	2	3.7
13 to 24 hours	0	—
1 to 5 days	16	30.1
6 to 10 days	9	16.9
11 days plus	14	26.4
Questionable	9	16.9

At necropsy the site of thrombosis was bilateral in 36 (67.9 per cent), right sided in nine (16.9 per cent) and left sided in eight (15.1 per cent). Actual infarction had developed in all except five instances. Four of these five patients died within 12 hours of the accident.

Thus, the experience in the Wisconsin General Hospital conforms rather closely with the conventional picture of pulmonary thrombosis. A rather dramatic phase of this vascular occlusion has apparently escaped clinical notice. The following clinical notes cover the essential features:

White laborer, 54 years old, was admitted with complaints caused by a chronic infectious arthritis. The evidences of congestive heart failure on an arteriosclerotic basis soon dominated the clinical course. The heart was enlarged to the left. A loud blowing systolic murmur was heard over the entire precordium and it was transmitted into the left axilla. The aortic second sound was accentuated and had a "bottom of well" quality. The peripheral vessels were thickened. The arterial blood pressure was 194 mm. Hg systolic and 120 mm. diastolic. Pulmonary congestion, hepatic engorgement and general anasarca completed the picture.

Under supportive measures the circulatory balance was steadily being restored when a startling change occurred. The patient suddenly experienced excruciating pain in the lower abdomen. Apprehension possessed him. Orthopnea and cyanosis supervened. The skin felt cold and clammy. In spite of immediate medical attention

he became pulseless, complained bitterly of continued pain, had an episode of explosive vomiting, and died within 20 minutes.

Necropsy revealed no vascular occlusion in the abdominal area. The pelvic vessels were free from evidences of thrombosis and embolism. Of interest were the generalized arteriosclerosis, involving particularly the aorta, the coronary and the renal arteries, and the atherosclerotic calcification of the right and posterior aortic valve

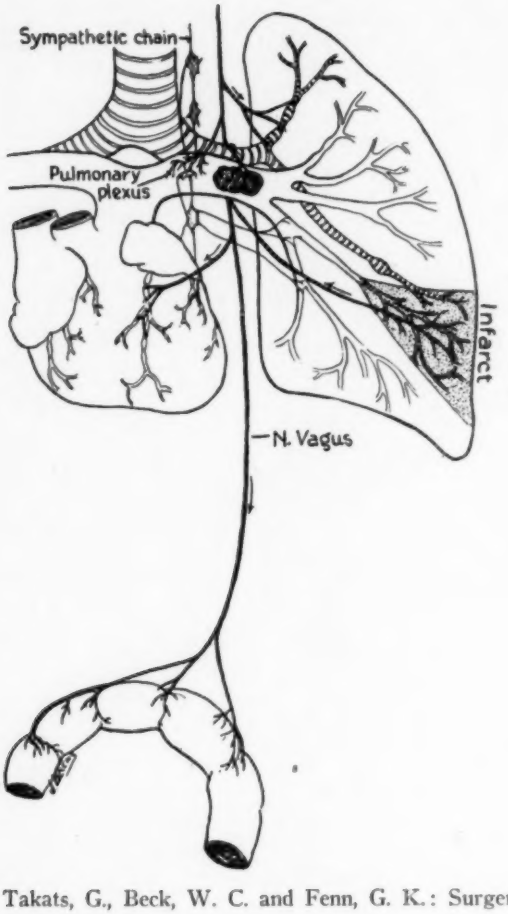

FIG. 1. (From de Takats, G., Beck, W. C. and Fenn, G. K.: Surgery, 1939, vi, 339.)

cusps. Most significant, however, was the extensive thrombosis of the pulmonary arteries. The branch of the pulmonary artery to the left lower lobe was occupied by a firm, white thrombus, and from this point there was extension of a red thrombus to the primary pulmonary artery. Adjacent divisions were occluded by a dark red, nonelastic thrombus in which areas of lighter color appeared. Histological study of the lung disclosed only passive congestion, slight hemorrhage and partial atelectasis.

The dramatic crisis of abdominal pain and collapse marking the sudden occlusion of a large branch or branches of the pulmonary artery has been encountered four times (three included in this series). A review of the literature discloses no exact parallel. Förster [3] defines a band-like, colicky

epigastric pain, succeeding pain in the left chest, in pulmonary thrombosis. Pou and Charr [4] refer to epigastric pain radiating into the substernal region in two patients (Cases 1 and 4). Many exhaustive reviews cite only thoracic distress and dull aching. The explanation is probably forthcoming in de Takats, Beck and Fenn's diagrammatic schema of the neurological impact of pulmonary occlusion (figure 1).[5] Interestingly they predict the possibility of upper gastrointestinal colic, increased peristalsis, and reverse peristalsis on this basis but adduce no clinical support.

In summary, this brief clinical note records an unusual and startling manifestation of pulmonary thrombosis, namely excruciating lower abdominal as well as epigastric pain with collapse. The attendant dyspnea and advancing cyanosis may lead to a correct interpretation. In one patient experiencing this sudden pain the simultaneous appearance of showers of fine moist râles in one base led to the accurate localization of the thrombus.

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TEN YEARS' EXPERIENCE WITH THOROTRAST HEPATOSPLENOGRAPHY *

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ALMOST 11 years ago we began to employ thorium dioxide sol intravenously for the purpose of demonstrating radiographically the liver and spleen as first used by Radt [1, 2, 3, 4] and Oka.[5, 6] Since that time we have used this method of diagnosis in more than 300 patients. This figure does not include the many cases of arterial and venous disease in which we have used smaller amounts of thorotrast ‡ for angiography.

In 1933 Yater and Otell [7] published a report of our clinical experience with 100 patients, and in 1936 Yater, Otell and Hussey [8] reported a follow-up study of 200 patients examined over a period of five years. This third report is a follow-up study of 286 patients examined over a period of more than 10 years, whose records were obtainable.

When we began to employ thorotrast hepatosplenography we were aware of two major problems in connection with this diagnostic procedure: (1) the possibility of the effects of latent radioactivity and other serious remote ill effects, and (2) the true value, finer points, and limitations of the method. It is hoped that the present report will help in some measure to elucidate these problems. It has been accepted, we believe, that serious immediate ill effects do not occur.

In recent years a large number of articles have appeared in the medical literature condemning the parenteral use of thorotrast because of supposed latent radioactivity or because of neoplastogenic properties of thorotrast deposited in the subcutaneous tissues. Practically all of these reports are based upon animal experimentation.

In 1938, Orr, Popoff, Rosedale and Stephenson [9] reviewed the subject and reported their experiments with rabbits. They found even minute amounts of injected tissue to be radioactive by means of histoshadowgrams and the spinthariscope. The use of filters showed that both alpha and gamma radiation were present. All histologic changes were attributed to the presence of thorotrast, of which the main ones were lesions in the liver varying from simple cloudy swelling to profound necrosis followed by fibrous tissue proliferation, degeneration or necrosis of the lymph follicles of the spleen, and hematopoietic depression of the bone marrow. From these studies they drew the following conclusions:

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‡ Thorotrast is the trade name given by the Heyden Chemical Company to its stabilized colloidal solution of thorium dioxide, which contains 25 per cent by volume of thorium dioxide.

1. Thorotrast is not eliminated from the body.
2. It apparently blockades the reticulo-endothelial system and may thus adversely affect a portion of the body's immunity mechanism.
3. It may profoundly damage the liver and spleen parenchyma with early and late degenerative changes.
4. It is a radioactive substance and undoubtedly has dangerous cumulative radioactive effects.

A few other articles may be mentioned as examples of the type of data upon which similar conclusions were based. In 1937 Taft,[10] using the Geiger counter, pointed out that a clinical dose of 75 c.c. of thorotrast possesses the gamma-ray activity of 1.37 micrograms of radium, and that thorium dioxide breaks down into mesothorium and radiothorium. This figure was in close accordance with that stated in 1932 by the Council on Pharmacy and Chemistry of the American Medical Association.[11] As little as 2 micrograms of radium has produced symptoms of radium poisoning (Martland[12]). Selbie[13] in 1938 reported that thorotrast given subcutaneously to rats and mice produced a tumor at the point of inoculation in 85 per cent of the rats and 26 per cent of the mice that lived for more than a year, spindle-cell sarcomata predominating. Foulds[14] in 1939 produced one carcinoma, two sarcomata, and one fibrosarcoma in three out of nine guinea pigs by injecting 0.2 to 0.3 c.c. of thorotrast into the base of the nipple, the average induction time being 37 months, and the first three tumors being transplantable.

In 1941 Stenstrom[15] reported a study of the radioactivity of the feces and breath of two patients who had received intravenous injections of 75 c.c. of thorotrast six and seven years previously and of the feces and urine of three rabbits in which 2 c.c. of thorotrast were injected into the veins of an ear, collections of urine and feces being made in the latter every few days for a long period of time. The study also included a determination of the amount of radioactivity of various organs of a rabbit which was killed 127 days after the injection of thorotrast. Radioactivity of appreciable amount was present in all specimens. Stenstrom concluded that "The presence of thorium in a living animal or patient can be revealed by means of gamma-ray measurements, but such measurements do not give quantitative values for the thorium. Thorium X is consistently found in the feces and thoron is exhaled in the breath. For quantitative determinations of the different radioactive elements in the thorium series it would be necessary to determine the range of the alpha particles and also to make beta-ray measurements. The relative amounts of the different elements depend to a certain extent upon the time elapsed since the thorium was concentrated. Excretion of thorium after intravenous injection of thorotrast in patients has not been discovered as yet and these studies show that a great portion of the thorium must have still remained in the tissues of two patients who received injections six and seven years prior to the measurements."

On the other hand, clinicians have not reported any serious ill effects as a result of the use of thorotrast. Rigler, Kouchy and Abraham [16] in 1935 published a follow-up study of 175 patients, of whom 22 had had the solution injected one, two or three years before without any ill effect. Reeves,[17] pointing out the value of thorotrast hepatosplenography in liver abscess in 1936, stated that in an experience of seven years he had not observed ill effects in patients. Koster,[18] demonstrating in 1940 the value of this method in three cases of pylephlebitis with liver abscess, noted that he had patients alive and not showing harmful effects three, four and five years after the introduction of the medium. Yater and Whitmore [19] in 1938 studied microscopic sections of the liver and spleen of 64 patients who had received thorotrast for varying periods of time before operation or death and were unable to find any evidence that the thorotrast had contributed to their death or that their organs showed damage that could be ascribed to its presence. One patient who had a nodule in the antecubital space resulting from the accidental subcutaneous injection of thorotrast more than four years before showed only a fibrous encapsulation of the thorotrast in a biopsy specimen of the tumor.

Technic of Hepatosplenography. Although thorium dioxide sol (thorotrast) has been used as a contrast medium for many purposes, it has been employed in the highest number of cases for hepatosplenography and for arteriography. For the latter purpose it has no peer. When injected into the blood stream thorotrast is removed rapidly and engulfed by the reticuloendothelial cells throughout the body. These cells, being numerous in the liver and spleen, allow these organs to be demonstrated on roentgenograms, because thorium, a metal of high atomic weight, is radiopaque. The average dose employed by us for this purpose has been 75 c.c., given intravenously, usually in divided doses of 25 c.c. on each of three successive days, the film being made on the fourth day. However, the entire amount may be given at one time without danger, and good films may be obtained as early as one and three-fourths hours later. In 1937 Yater [20] showed that with this single dose of thorotrast the contrast medium is engulfed by the reticuloendothelial cells of the liver and spleen as early as 15 minutes after the injection in sufficient amount to allow a shadow to be cast by these organs on the roentgenogram, and that films made after one and three-quarters hours show only slight improvement. Good films are usually obtainable with the patient placed in the prone position by means of the following technic: 300 M.A.; K vp. 58; distance 40 inches; time ¼ to ½ second, depending on the size of the patient. It is important that thorotrast not be injected subcutaneously, since a hard fibrous nodule results which may become painful at times and which may make subsequent use of the vein difficult.

In good films the normal liver casts a homogeneous shadow of approximately the same density as the spine, but occasionally the normal liver shows a very fine mottling, which, however, is much more delicate than

that seen in cases of cirrhosis (figure 1). The normal spleen has a density slightly less than that of the liver and about the same as that of the ribs. Although we measure the liver and spleen in centimeters,[7] a good idea of the relative size as compared to normal and to subsequently made films is gained by simple inspection.

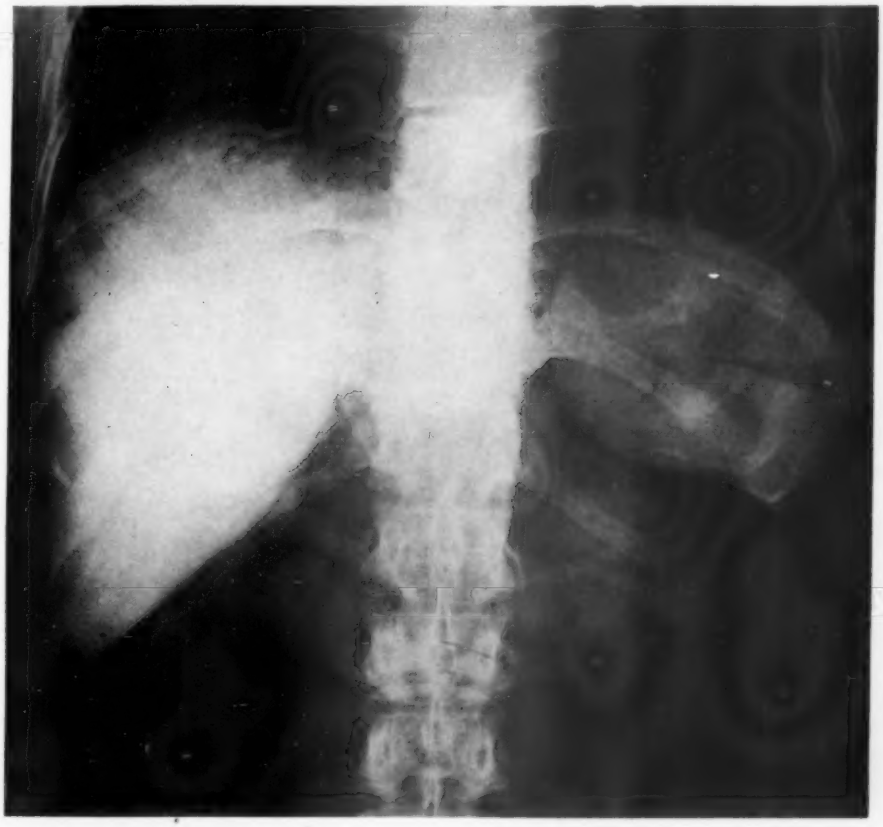

FIG. 1. Normal hepatosplenogram.

Follow-up Study of 189 Patients Who Died. Of the patients who could be traced at this time 189 are known to be dead. These included 119 males and 70 females; and 104 were white patients, 84 colored patients, and 1 Filipino. At the time of injection of thorotrast seven patients were in the first decade of life, two in the second decade, seven in the third decade, 46 in the sixth decade, 40 in the seventh decade, 17 in the eighth decade, and two in the ninth decade; in two cases the ages could not be found. The majority of the patients were given 75 c.c. of thorotrast; children were given relatively smaller amounts, and some adults received 40 or 60 c.c.

In 70 cases necropsy was performed, and in a number of cases surgical coeliotomy was performed. Of the patients who came to necropsy 40 had

carcinoma or other malignant neoplasia, 17 had cirrhosis of the liver, and the other 13 had such miscellaneous conditions as myeloid leukemia, tuberculosis, disease of the heart, pernicious anemia, sickle-cell anemia, and bacterial endocarditis. The clinical diagnoses in the cases in which necropsy was not performed were cancer or other malignant neoplasia in 46, cirrhosis of the liver in 28, leukemia in eight, congestive heart failure in five, hepatitis in three, tuberculosis in three, and such miscellaneous diseases in the remaining 26 as amebic liver abscess, hemochromatosis, hepatoma, polycystic kidneys, subphrenic abscess, and ruptured spleen. All of the 189 patients had diseases serious enough in themselves to account for death, and in none could the thorotrast be in any wise considered a factor in either causing death or precipitating it.

There were 16 patients who died within 24 hours of the administration of thorotrast, 17 who died between 24 hours and one week, 51 who died between one week and one month, 49 who died between one month and six months, 14 who died at the end of a year, and 29 who lived from one year and three months to eight years and three months. In 13 cases the information available did not allow an accurate determination of the time elapsed.

Of the 29 patients who lived more than one year and three months, there were nine who lived between one and two years, eight between two and three years, four between three and four years, two between four and five years, two between five and six years, three between seven and eight years, and one more than eight years. Ten of these 29 patients had cirrhosis of the liver, and in four cases the diagnosis was verified by necropsy. These patients lived from one year and eight months to eight years and three months after the administration of thorotrast. One of them lived seven years and another eight years and three months. The one who lived seven years was 42 years old at the time of the first examination in December, 1935. He was an Italian tile setter who had noticed progressive enlargement of the abdomen for more than a year. He did not drink immoderately. He was found to have a greatly enlarged liver, and the hepatosplenogram showed the typical appearance of hypertrophic cirrhosis with a moderately enlarged spleen. A year later he was seen again. This time he was moderately jaundiced, his liver was still greatly enlarged and his spleen was then palpable. A bromsulfalein test showed 50 per cent retention at the end of 5 minutes and 15 per cent at the end of 30 minutes. The quantitative Van den Bergh test was 5 mg. per 100 c.c. of blood. The hepatosplenogram had not changed. In January 1942 this patient was hospitalized and was found to be moderately icteric and to have ascites and an enlarged liver. His hepatosplenogram showed many large rounded opaque masses within and adjacent to the liver shadow, evidently lymph nodes filled with thorotrast. He died in six weeks and necropsy revealed typical Laennec's cirrhosis of the liver. Another patient, who lived five years and one month after the administration of thorotrast, when she was 71 years old, had typical syphilitic

cirrhosis of the liver with lobulation at that time. The liver and spleen were both enlarged, and there were many large collateral veins. The necropsy revealed a small, firm, coarsely nodular liver and a moderately enlarged spleen; there was a small amount of ascites but no jaundice.

Other interesting patients in this group were one with chronic lymphatic leukemia who lived one year and six months, one with chronic myeloid leukemia who lived two years and four months, one with lymphosarcoma who lived one year and 10 months, one with carcinoma of the ampulla of Vater who lived one year and 11 months, and one with mitral stenosis who lived seven years and five months and died of subacute bacterial endocarditis.

Report of 67 Patients Who Could Not Be Traced. There were 67 patients whose records were available but who could not be traced at this time. The age, sex and color incidence were approximately the same as in the group of patients who were known to have died. It is probable that many of these untraced patients had also died, since 10 were given the diagnosis

TABLE I

Pertinent Data of 30 Rechecked Patients

Case No.	Sex	Color	Age When First Examined	Diagnosis	Number c.c. of Thorotrast	Time Since Injection	Bromsulfalein Test at Last Examination *	General Condition
1	Female	White	58	Chronic lymphatic leukemia	60	10 years, 5 months	Not satisfactory because of veins	Good
2	Male	White	60	Syphilitic aortitis	50	10 years, 6 months	Refused	Good
3	Female	White	28	Hepatitis with jaundice and ascites	60	10 years, 5 months	70% and 0%	Good
4	Male	White	37	Diabetes and carotinemia	75	10 years, 1 month	60% and 5%	Had "stroke" 1 year ago
5	Female	White	36	Syphilitic cirrhosis	75	10 years	55% and 5%	Working; had baby in 1935
6	Male	White	3	Xanthomatosis	25	10 years	10% and 5%	Well; repeated roentgen-ray treatments
7	Female	White	49	Cirrhosis	60	10 years	50% and 5%	Good
8	Male	White	25	Hemolytic jaundice	25	10 years	60% and 0%	Good but jaundiced
9	Male	White	33	Exophthalmic goiter	75?	10 years	25% and 10%	Good, drinking excessively
10	Female	White	32	Catarrhal jaundice	75	9 years, 9 months	Not satisfactory	Dementia praecox, otherwise good
11	Male	Colored	55	Syphilitic cirrhosis	75	9 years, 8 months	60% and 20%	Good but not working
12	Female	White	60	Hepatitis	75	9 years, 6 months	55% and 0%	Good
13	Female	White	5	Thrombosis of splenic vein	15	9 years, 6 months	Not done	Good
14	Male	White	49	Hepatitis	75	9 years, 3 months	70% and 5%	Moderately good
15	Female	White	9	Possibly ruptured spleen	8	9 years, 2 months	Not satisfactory because of veins	Good

TABLE I (*Continued*)

Case No.	Sex	Color	Age When First Examined	Diagnosis	Number c.c. of Thorotrast	Time Since Injection	Bromsulfalein Test at Last Examination *	General Condition
16	Female	White	35	Syphilitic cirrhosis	75	8 years, 9 months	Not done	Good
17	Male	White	45	Polyserositis	75	8 years	80% and 5%	Moderately good
18	Female	White	65	Suspected cancer of stomach (eliminated by operation)	75	7 years, 4 months	30% and 0%	Good
19	Male	White	42	Transient ascites	75	7 years, 3 months	Not done	Good
20	Male	White	78	Cholecystitis	50	6 years, 2 months	Not done	Good
21	Male	Colored	48	Thromboangiitis obliterans	100	6 years, 1 month	30% and 0%	Good
22	Male	Colored	56	Gangrene of foot	Not recorded	6 years	90% and 5%	Moderately good
23	Male	Colored	32	Thromboangiitis obliterans	60	5 years, 10 months	5% at end of 1 hour	Good
24	Female	White	33	Hepatitis with jaundice and ascites	75	5 years, 4 months	70% and 20%	Good
25	Female	Colored	62	Hepatitis with jaundice and ascites	75	4 years, 3 months	50% and 10%	Good
26	Female	White	43	Cirrhosis	75	3 years, 5 months	90% and 5%	Good
27	Male	White	36	Carcinoma of colon	75	2 years, 9 months	Not done	Good and working
28	Male	White	44	Amebic abscess of liver	75	Less than 1 year	Not done	Good
29	Male	White	47	Amebic abscess of liver	75	Less than 1 year	Not done	Good
30	Female	White	40	Cirrhosis?	75	Less than 1 year	30% and 0%	Bedridden from peripheral neuritis

* All bromsulfalein tests were performed by original method of injecting 2 mg. per Kg. of body weight and taking specimens of blood at intervals of 5 minutes and one-half hour, except in case 22, in which 5 mg. per Kg. were injected and blood examined at end of 1 hour.

of carcinoma, 17 cirrhosis of the liver, three leukemia, three tuberculous peritonitis, one Hodgkin's disease, two congestive heart failure, and three sickle-cell anemia. There were 13 patients in this group who had been rechecked at varying intervals since the administration of thorotrast. Among these were four cases of cirrhosis of the liver in which reëxaminations had been made at intervals of one year, one year and nine months, and three years and eight months. A patient with syphilitic cirrhosis was seen two years and two months after the administration of thorotrast. Other cases were hyperthyroidism (three years), chronic myeloid leukemia (three years and four months), sickle-cell anemia (three years and nine months), appendiceal abscess (four years), abscess of the liver (four years and two months), and purpura hemorrhagica (four years and four months). A patient for whom a definite diagnosis could not be made was rechecked at the end of two years and three months.

Recheck of 30 Living Patients. At present there are 30 patients still under observation. All but four of these have been reëxamined very recently; the four not examined are known to be alive and well. A tabulation of pertinent data of these cases is given in table 1. There were nine patients who were living and well (for practical purposes) 10 years or longer following the injection of thorotrast, six after nine years, two after eight years, two after seven years, three after six years, two after five years, one after four years, one after three years, and one after two years and nine months. Three patients have Laennec's cirrhosis of the liver, three have syphilitic cirrhosis of the liver, six had severe hepatitis at the time of injection of thorotrast (three with ascites), and two had recovered from amebic abscess of the liver (one following operation and one following spontaneous drainage through a bronchus).

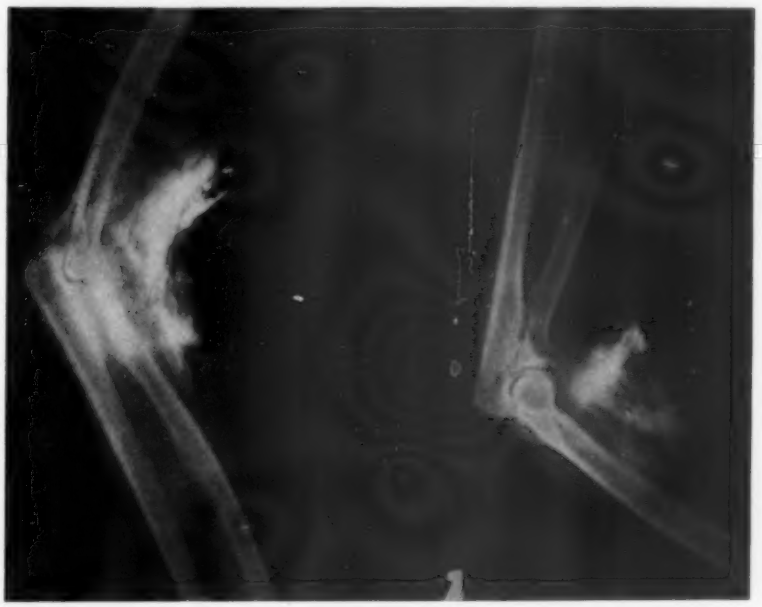

FIG. 2. *Case 1.* Thorotrast in subcutaneous tissues of arms 10 years and 5 months after injection.

The remarkable point concerning this series is the fact that patients who had or have had serious disease of the liver in most instances have lived longer than was anticipated and have continued in moderately good health. There were three patients who had jaundice with ascites at the time of injection of thorotrast. Many other patients in the entire series had jaundice when the medium was administered.

A point worth emphasizing is that a review of these cases showed that the patients had fewer attacks of infectious diseases including colds than individuals of the general population. There was certainly no evidence

that the presence of thorotrast in the reticulo-endothelial cells depressed the immunity mechanism of the body.

Illustrative Cases

Case 1. Miss M. B. C., now aged 69 years, was found to have chronic lymphatic leukemia in July, 1930. The first hepatosplenogram was made on July 16, 1931, following the injection of 60 c.c. of thorotrast. Roentgen-ray therapy caused the blood picture to return to normal, and she has required such therapy only once since then. She has remained well to date (December 11, 1941), 10 years and 9 months,

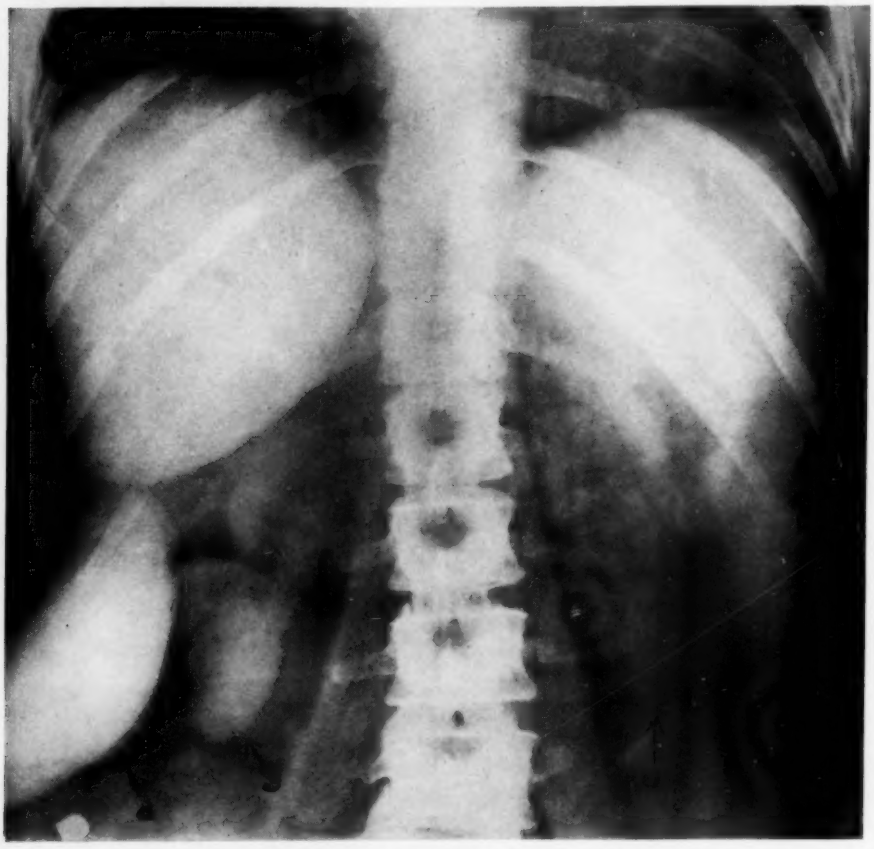

Fig. 3. *Case 1.* Original hepatosplenogram made July 16, 1931, showing Riedel's lobe, moderately enlarged spleen, and well shown kidneys (chronic lymphatic leukemia).

with only an occasional upper respiratory infection and minor complaints. The white blood cell count is 19,900 per cu. mm. of blood with 51 per cent lymphocytes but no blast forms. Some of the thorotrast was injected accidentally in the subcutaneous tissues of both arms, causing nodular swellings. These are firm and unsightly but the patient refuses to have them excised (figure 2). They have not enlarged. The original hepatosplenogram showed some enlargement of the liver and moderate enlargement of the spleen (figure 3). The last film, made on April 17, 1942, shows

the liver to be somewhat smaller, homogeneous, but of moderately reduced density (figure 4). The spleen is about the same size and less dense. A small lymph node containing thorotrast is visible on the right side of the first lumbar vertebra; it was first observed in April, 1935.

FIG. 4. *Case 1.* Hepatosplenogram made 10 years and 9 months after the first, showing moderate diminution in density of liver and spleen but no change otherwise except for a small opaque lymph node between liver and spine.

Case 2. Mrs. I. D., now aged 59, had hepatitis with severe jaundice for several weeks in November, 1931. Biopsy of the liver showed a chronic fibrosing process with a superimposed acute one characterized by large areas of leukocytic infiltration. A bromsulfalein test of liver function after recovery from the acute hepatitis showed 50 per cent retention after five minutes and none at the end of 30 minutes. On February 4, 1932, after injection of 60 c.c. of thorotrast, hepatosplenograms showed the liver to be quite small, the medium well concentrated, and no apparent alteration of structure. The left lobe was large, compared with the right. The spleen was normal in size and density. Except for various intermittent complaints, such as dyspepsia and headaches and a rare "cold," she had been well, and physical examination on May 24, 1937, was essentially negative. A liver function test performed on October 10, 1936, gave results identical with the original one. A hepatosplenogram, made May 24, 1937, more than five years after the first showed the liver and spleen to be about the same size as originally but there was great mottling and moderate reduction in density of both organs, indicative of elimination of the contrast medium, and very dense shadows of upper abdominal lymph nodes to which the mobilized thorotrast had migrated. The last check-up was made on February 12, 1942, just 10 years after the injection of thorotrast. She had continued to be well except for minor complaints and a sore near the base of the tongue. A bromsulfalein

test showed 50 per cent retention at the end of five minutes and 5 per cent at the end of 30 minutes. A hepatosplenogram shows slightly less density of the liver than originally with mottling due to mobilization of the thorotrast, and dense lymph nodes in the region of the porta hepatis (figure 5). The left lobe appears to be larger than the right. The spleen is dense and perhaps a little smaller.

Case 3. M. A., a white woman now 38, had a prolonged illness in the fall of 1931 accompanied for a while by severe jaundice and ascites which gradually disappeared. Biopsy of the liver showed a subacute inflammatory process. After recovery, the bromsulfalein test showed 75 per cent retention in five minutes and 15 per cent in 30 minutes. Hepatosplenograms made December 10, 1931, after injection of 60 c.c. of thorotrast, showed the liver and spleen to be of normal size, but the liver was finely mottled. Physical examination on April 2, 1937, was essentially negative. She had gained 20 pounds. The liver function test showed 35 per cent retention in five minutes and none after 30 minutes. The hepatosplenogram showed linear and granular mottling of the liver and spleen, indicative of mobilization of thorotrast, and visible lymph nodes between the two organs. The patient has continued to be well and is getting fatter. The last physical examination made on March 13, 1942, more than 10 years after the injection of thorotrast, was negative. A bromsulfalein test showed 70 per cent retention at the end of five minutes and none at the end of 30 minutes. A hepatosplenogram looks the same as formerly with somewhat less density of the liver and spleen (figure 6).

Case 4. Mr. F. S., now aged 47, was found to have diabetes mellitus in 1931. Dietetic treatment caused carotinemia. Hepatosplenograms made on February 6, 1932, after injection of 75 c.c. of thorotrast, showed normal hepatic and splenic shadows. The patient has been very well. Hepatosplenograms made on May 24, 1937, more than five years after the first, showed some diminution in density and mottling of the liver and spleen, and lymph nodes were visible in the upper abdomen. Since then the patient has been well except for a stroke in 1937 with residual hemiparesis. Examination on March 6, 1942, more than 10 years after the injection of thorotrast, was otherwise negative. A bromsulfalein test showed 60 per cent retention at the end of five minutes and 5 per cent at the end of 30 minutes. The hepatosplenogram shows somewhat less density.

Case 5. Miss L. B., now aged 18, was run over by an automobile on November 30, 1932, suffering shock and severe pain in the upper left quadrant of the abdomen. To determine whether the spleen was ruptured 8 c.c. of thorotrast were injected and a hepatosplenogram made three hours later. This showed the spleen to be intact. Recovery ensued without a surgical operation. The patient has remained well and developed normally. A hepatosplenogram made on May 3, 1937, showed very dim shadows of the liver and spleen with diffuse granular mottling of the latter and visible lymph nodes near the porta hepatis. Some thorotrast had been accidentally injected into the subcutaneous tissues of both arms and small firm nodules had resulted. These did not cause trouble and were painful only when the arm was squeezed. One was removed for microscopic study and was found to be composed of dense hyaline connective tissue encapsulating clumps of thorotrast. This patient has remained well, and a hepatosplenogram made on February 25, 1942, more than nine years after the injection of thorotrast, shows very little contrast medium in the liver, but the spleen is about as dense as on the previous examination.

Case 6. Mrs. D. M., now aged 46, was found to have syphilis 22 years ago, and treatment has been given intermittently since that time. Dyspepsia developed, and in January, 1931, the liver and spleen were found to be enlarged. In October, 1932, the liver was considerably enlarged, firm and irregular; the spleen was also moderately enlarged. A bromsulfalein test showed 45 per cent retention at the end of five minutes and none after 30 minutes. Hepatosplenograms made on March 22, 1932,

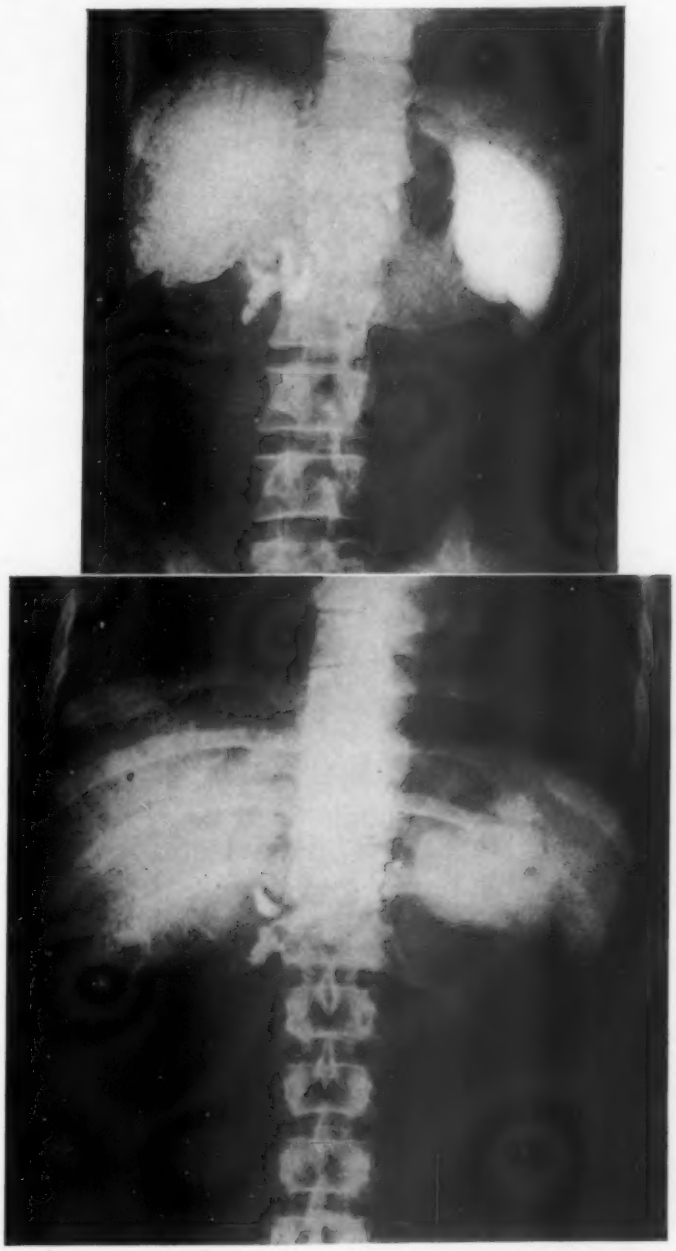

FIG. 5 (above) *Case 2.* Hepatosplenogram made 10 years after injection of 60 c.c. of thorotrast in a case of cirrhosis of the liver, showing the rather small right lobe and the enlarged left lobe of the liver which is mottled because of mobilization of thorotrast. The spleen is not enlarged but is quite dense; an accessory spleen is shown. A large group of lymph nodes containing thorotrast is demonstrable.

FIG. 6 (below) *Case 3.* Hepatosplenogram made more than 10 years after the first which was made following recovery from an attack of jaundice with ascites. Shadows are somewhat decreased in density, spleen is mottled, and adjacent lymph nodes are shown.

after the injection of 75 c.c. of thorotrast, showed the typical picture of hepar lobatum with splenomegaly (figure 7). In October, 1935, she delivered a normal baby. She has been working since then, but she has frequent nosebleeds and tires easily. On May 19, 1937, the physical examination was essentially the same as in 1932. The liver function test showed 50 per cent retention after five minutes and 5 per cent after 30 minutes. Wassermann and Kahn tests of the blood were strongly positive. The hepatosplenogram showed extensive, irregular coarse mottling of the liver due to mobilization of the contrast medium, many visible lymph nodes in the

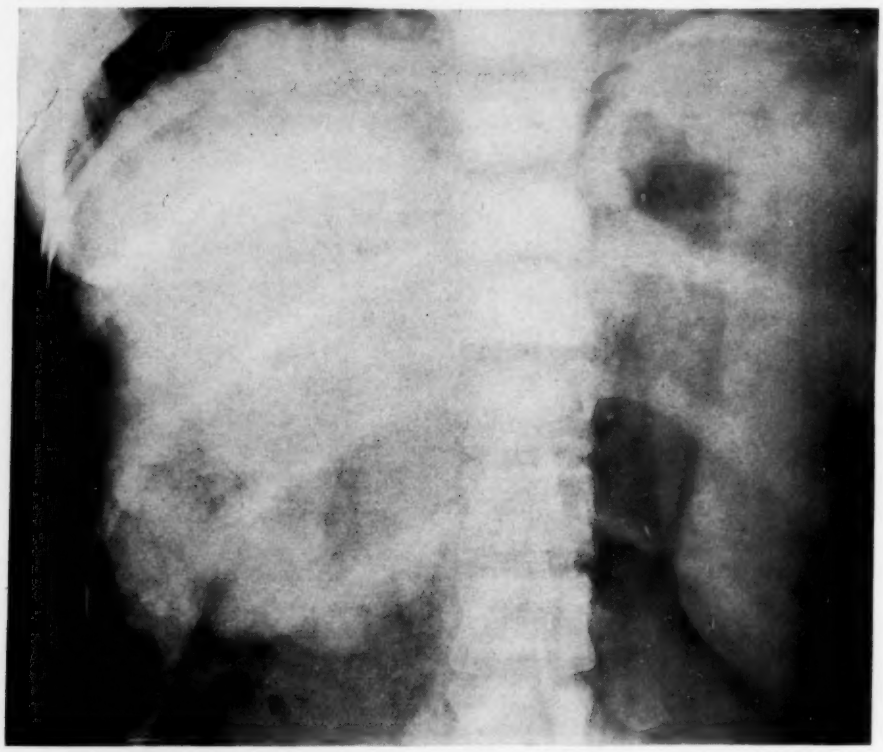

FIG. 7. *Case 6.* Hepatosplenogram made on March 22, 1932, after injection of 75 c.c. of thorotrast, showing mottled and lobulated liver (hepar lobatum) with splenomegaly.

upper abdomen, and still considerable density of the enlarged spleen. In 1941 the patient became weak and very anemic because of excessive uterine bleeding. Menopause was induced by irradiation and blood transfusions and iron given in December, 1941. In January, 1942 she returned to work. The physical examination is the same as formerly. A bromsulfalein test showed 55 per cent retention at the end of five minutes and 5 per cent at the end of 30 minutes. A hepatosplenogram, made 10 years after the first, appeared the same as in 1937 (figure 8).

Case 7. Mrs. G. B., now aged 70, had a severe attack of jaundice in April, 1932. Cholecystostomy was performed, followed by recovery. A hepatosplenogram, made May 7, 1932, after injection of 75 c.c. of thorotrast, showed normal hepatic and splenic shadows. The patient has been well since then except for minor ailments. The last hepatosplenogram, made December 1, 1941, nine and a half years after the first, shows some diminution in density of the liver and spleen with mottling and visible

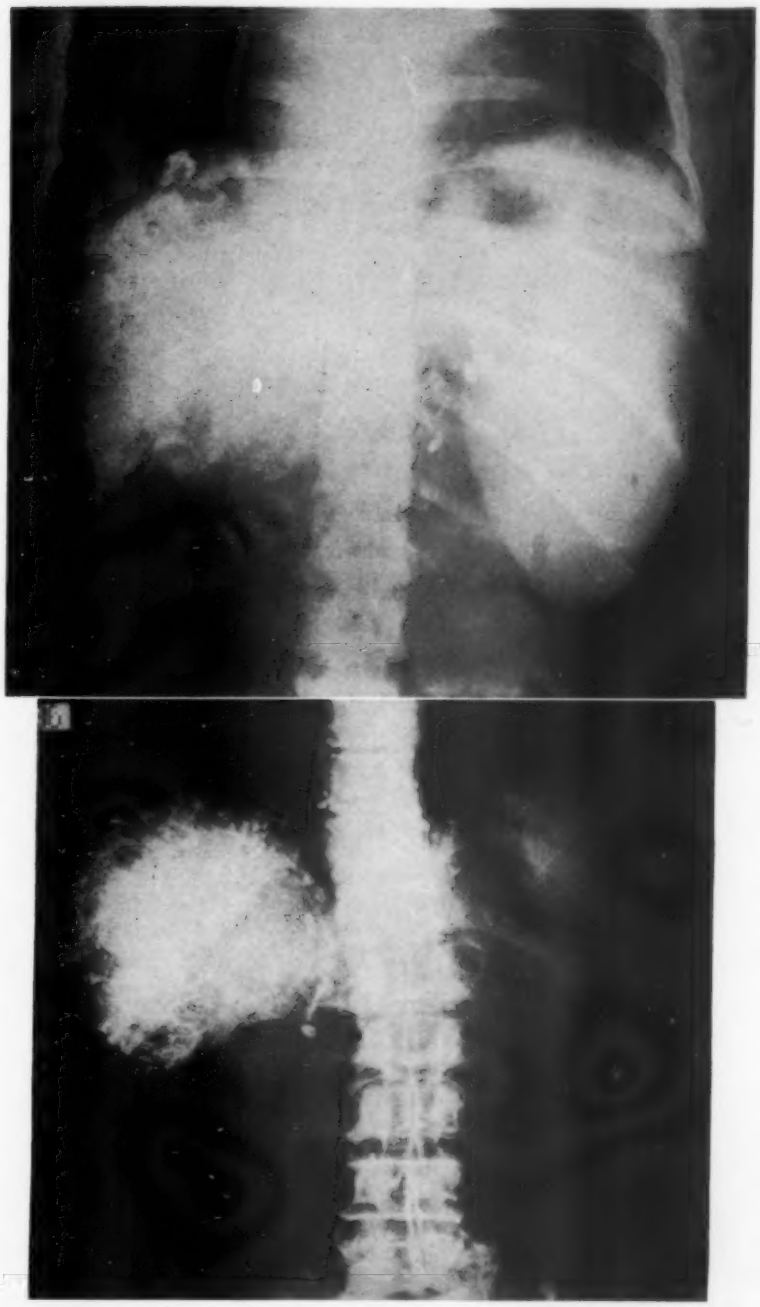

FIG. 8 (above) *Case 6.* Hepatosplenogram made December 1, 1941, nearly 10 years after the first, showing gross and irregular mottling of the liver due to the mobilization of thorotrast. Many lymph nodes containing mobilized thorotrast are visible. The spleen is still enlarged and quite dense.

FIG. 9 (below) *Case 12.* Hepatosplenogram of a case of syphilitic cirrhosis of the liver made 9 years and 8 months after injection of 75 c.c. of thorotrast, showing irregularity of liver outline and irregular mottling. The spleen is of reduced density and not enlarged. Periportal lymph nodes are visible.

lymph nodes in the upper abdomen. A bromsulfalein test on March 18, 1942 showed 55 per cent retention at the end of five minutes and none after 30 minutes.

Case 8. E. C., a white boy, now aged 13, was found to have xanthomatosis in 1931. A hepatosplenogram made on March 24, 1932 after injection of 25 c.c. of thorotrast, showed normal shadows for liver and spleen. Under roentgen-ray therapy he has improved greatly. A hepatosplenogram made on February 17, 1942, nearly 10 years after the first, shows considerable diminution in density of the liver and spleen with mottling and a visible lymph node near the porta hepatis.

Case 9. J. C., a white man, now aged 72, was first examined in September, 1931. He had syphilitic aortitis, and because of an enlarged spleen a hepatosplenogram was made (Sept. 8, 1931), after the injection of 50 c.c. of thorotrast. This showed a normal liver. He has remained well, receiving antisyphilitic treatment. Examination on March 5, 1942, showed merely aortic regurgitation. The spleen was not palpable. A hepatosplenogram, made 10 and a half years after the first, shows the spleen to be slightly enlarged; both the liver and spleen are finely mottled, and there is a small amount of thorotrast in the adjacent lymph nodes.

Case 10. F. E., a white man, now aged 43, was found to have exophthalmic goiter in 1932. A hepatosplenogram was made on March 25, 1932, after the injection of 75 c.c. of thorotrast with the idea of determining whether in this disease the spleen was contracted. The film was normal. Ten years later the patient, who had had a subtotal thyroidectomy, was found to be well, although he had become a moderate alcoholic. A bromsulfalein test showed 25 per cent retention after five minutes and 10 per cent at the end of a half hour. The hepatosplenogram shows the liver and spleen to be of normal size. Only a small amount of thorotrast seems to be retained in these organs, but there is the usual concentration of it in the adjacent lymph nodes.

Case 11. B. C., a white woman, now aged 42, had catarrhal jaundice in 1932. A hepatosplenogram made on June 1, 1932 showed the liver to be normal and the spleen moderately enlarged. She later developed dementia praecox, but remained well otherwise. Reëxamination on March 14, 1942, after nine years and nine months, showed the usual changes in distribution of the thorotrast.

Case 12. J. G., a colored man, now aged 65, had jaundice, ascites, and an enlarged liver in 1932. A hepatosplenogram made on June 16, 1932 after the injection of 75 c.c. of thorotrast showed questionable evidence of syphilitic cirrhosis. The patient has remained well except for the development of diabetes mellitus. He has received antisyphilitic treatment. A physical examination on February 10, 1942 was negative, and a bromsulfalein test showed 60 per cent retention at the end of five minutes and 20 per cent at the end of 30 minutes. The hepatosplenogram, made nine years and eight months after the first, shows a lobulated liver with irregular distribution of the thorotrast (figure 9). The medium is concentrated in the splanchnic lymph nodes. The spleen is faintly visible and is normal in size.

Value of Hepatosplenography in Diagnosis. As the years have passed we have become more conservative in the use of this method of diagnosis because of better selection of cases. During the first few years we were attempting to learn all we could about it and were using it in all cases of hepatomegaly, splenomegaly, and undetermined masses in the upper abdomen, and in cases of suspected cirrhosis or possible metastases to the liver. Experience has shown that it is of little value in cases of splenomegaly. Its greatest usefulness is in helping to diagnose early cases of cirrhosis of the liver, metastases in the liver, and abscess of the liver. In the series reported there

were four cases of solitary abscess of the liver, all positively diagnosed by hepatosplenography (figure 9). Cirrhosis and metastases have been confirmed many times by this method of diagnosis. Cirrhosis of the liver is indicated by diffuse mottling or reduced density of the liver, often with changes in size or configuration of the organ. Metastases in the liver are denoted by rounded areas of lessened density surrounded often by a halo of increased density. Abscess produces a rounded area of reduced density, usually without the halo.

Little help has been obtained from follow-up films. The usual change is diffuse punctate or interlacing linear mottling and opacity of upper abdominal lymph nodes due probably to migration of Kupffer cells laden with thorotrast from the liver and spleen to their adjacent lymph nodes. In a few cases some of the thoracic lymph nodes have shown evidence of thorotrast deposition. In one case it appears as if there is thorotrast in both hemidiaphragms. In only three cases has the spleen become importantly reduced in size with increased density. In some cases of cirrhosis of the liver that organ has become smaller. In comparing films, due consideration must be made for even slight differences in technic.

As to the correctness of diagnosis by hepatosplenography, review of our 286 cases shows that the diagnosis of conditions of the liver was correct or very probably correct in 159 instances, incorrect in 10, and unsatisfactory (because of technical or other difficulties) in 25; in 92 cases it was impossible to verify the diagnosis by necropsy, operation or subsequent course.

Summary and Conclusions

A report has been made of the use of thorotrast hepatosplenography in 286 cases over a period of more than 10 years. Of these patients 10 were known to have lived for more than 10 years, 5 between 9 and 10 years, 3 between 8 and 9 years, 5 between 7 and 8 years, 3 between 6 and 7 years, 4 between 5 and 6 years, 6 between 4 and 5 years, 10 between 3 and 4 years, 10 between 2 and 3 years, and 12 between 1 and 2 years. No immediate or remote ill effects of importance have been observed. There has been no evidence of latent radioactivity, depression of hepatic or splenic or hematopoietic function, lowered resistance to infection, or development of malignant neoplasia at the site of injection.

Hepatosplenography is of definite value (1) in helping to diagnose cirrhosis of the liver, (2) to determine the presence of metastases in the liver, and (3) in the diagnosis of abscess of the liver.

Care should be taken to inject thorotrast into the veins and not into adjacent tissues, not because of the possibility of the development of neoplasms, but in order to prevent the formation of nodules and to save the veins.

The authors wish to express their gratitude to Dr. Richard H. Meredith, fellow in medicine, Dr. Philip S. Arthur, fellow in radiology, and Mrs. Alice Eldred Bond, secretary, for their assistance in accumulating records and films and reëxamining patients.

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A RECORDING SPHYGMOTONOGRAPH: A MACHINE FOR THE CONTINUOUS RECORDING OF SYSTOLIC AND DIASTOLIC ARTERIAL PRESSURE IN MAN*

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IN nearly all branches of medicine the problem of continuously recording the human blood pressure arises from time to time. There are many perplexing problems, the solution of which would be materially furthered by having a continuous record of the variations in systolic and diastolic pressure. In 1928 we were confronted with the following question: does the blood pressure rise, in certain types of angina pectoris attacks, prior to the attack and thereby become a provocative factor of coronary insufficiency, or does the rise merely represent a consequence of the pain and the anxiety? The answer to this query depended upon the ability continuously to follow the pressure changes occurring over long periods of time. Moreover, for years there have been demands for such a device on the part of anesthetists,[1] surgeons,[2] and gynecologists who desired to obtain a better impression of the changes occurring during the whole course of the preoperative, operative and the postoperative periods. Psychiatrists[3] and psychologists[4] also have desired to estimate the influence of psychic emotions on pressure changes over long periods of time.

It was the aim of our experiments to devise an instrument which would give correct and continuous records of the systolic as well as the diastolic blood pressure and which would not need an expert operator nor result in tracings which required further interpretation. The machine should be universally applicable without adjustments.

After four years of experiments, we published our first report on such an apparatus.[5, 6] The principle of this device can be summarized as follows (figure 1):

A double-bag cuff, with a total width of 12 cm. for both bags, is applied to the arm of the person being examined. The cuff is connected to a supply of compressed gas. This connection can be interrupted electrically by a solenoid pinching valve, thus interrupting the ascent of pressure in the cuff. The lower bag of the cuff, which is connected to the upper through a very narrow orifice, has another opening leading into a nozzle, through which the air from the lower bag can blow against an instrument which transforms the puffs of air into equivalent "puffs" of current. These electric currents, sent through an amplifier or a system of sensitive relays, are used to

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open or close the above mentioned solenoid valve. Since there is a small leak in the line to the upper cuff, some air can always escape from the system.

The principle of the measuring process is the following:

The device is switched into the diastolic position in which the solenoid valve is normally *open* until it is energized; then an impulse from the lower cuff appears and causes its closure. In the region below the diastolic pressure, for reasons to be explained further on, no impulse will occur from the lower cuff. When the diastolic pressure is reached, the first impulse of sufficient steepness occurs in the lower cuff; this activates the detecting

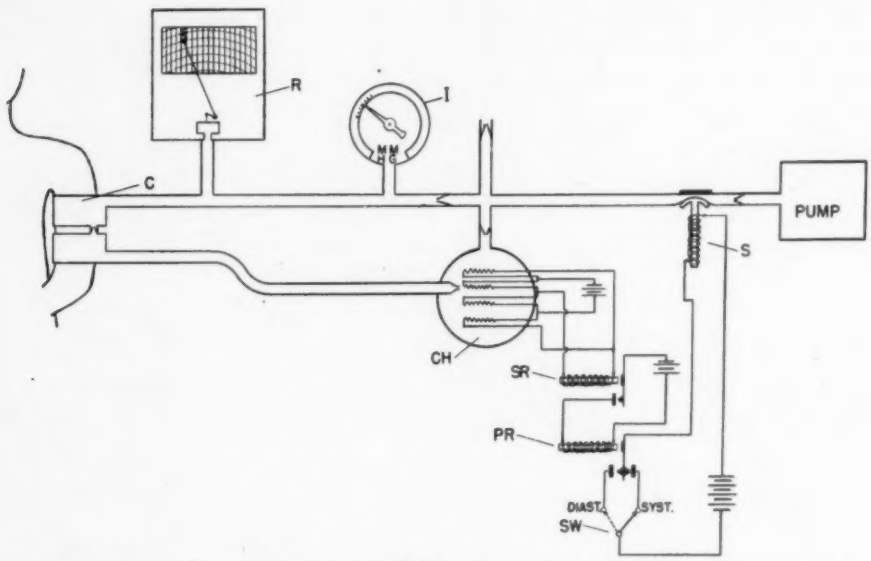

FIG. 1. Principle of the sphygmotonograph. S = solenoid pinching valve, I = indicating instrument, R = recorder, C = double cuff, Ch = chamber containing the set of nickel coils, SR = sensitive relay, PR = power relay, SW = diast.-syst. switch.

instrument causing the solenoid valve to close, so that no compressed gas is now supplied to the cuff. This permits some air to escape through the leak and the pressure in the system to fall until a level is obtained at which no further impulses occur. Since, at this point, there is no activation of the valve, the valve automatically opens and again compressed gas is supplied to the cuff system, thus repeating the procedure. A recording and an indicating instrument are connected with the line leading to the upper cuff, giving a continuous tracing of the changes in pressure. If a systolic recording is desired instead of the diastolic, the switch is thrown over into the systolic position; in this position the solenoid valve is normally closed and opens only when an impulse is given to the sensitive instrument from the lower cuff. In the region between the diastolic and the systolic pressure every pulse causes such an impulse and thereby opens the valve and allows

compressed gas to enter the cuff system. The moment the peak of the systolic pressure has been passed, further impulse ceases, the valve closes automatically, and the leak slowly releases the pressure. When the first pulse reappears in the lower bag of the cuff, an impulse again opens the valve and allows pressure to enter the cuff, until once again impulses to the lower cuff are eliminated. This procedure, too, is recorded and indicated by the instruments.

Since our original publication, this basic principle has been applied and copied, with more or less success, by a great number of other investigators.

In 1920, unknown to us, Kolls [7] had employed a somewhat similar idea to record the systolic pressure alone. His system had some of our features, but the lower cuff in his device was always fixed at a constant pressure of about 100 mm. Hg. The chief disadvantage of his method resides in an inability to obtain readings of the diastolic pressure and to follow fluctuations of the systolic pressure which go below 100 mm. Hg, in which case his lower cuff acted as an occlusive cuff and ceased to act as an oscillation indicator. Furthermore, the impulses from his lower cuff were transmitted to a simple contact instrument by a tambour, a system which we tried but soon abandoned on account of its unreliability.

Koch and Simon [8] tried a procedure absolutely different from ours. They put the arm into a plaster of Paris cast and placed a rubber balloon in the hand of the patient. Fluctuations of the blood pressure were recorded from this rubber bag which was filled with compressed gas.

In 1936 Omberg [9] altered our principle by using a microphone to activate the solenoid valve through an amplifier as soon as a sound distal to the cuff appeared or disappeared. We already had rejected this device several years prior to this time because of the difficulty in placing the microphone on the correct point and because of the high disturbance level of such a microphone when it is sufficiently sensitive to register the first faint sounds. Since it is often very difficult, even for the trained ear, to decide which is the first actual sound caused by a pulse wave passing under the cuff, a microphone, with no possibility of selection, very often gives misleading results.

In 1937 Stokvis [10] copied our device in all its details save for a simple contact set-up, and reported that he obtained satisfactory results with it. We cannot understand how absolutely exact diastolic readings can be obtained by a simple contact instrument for the transformation of impulses from the lower cuff into activating currents. Moreover, a container connected to the upper cuff for the purpose of reducing the shock-like action of the device naturally must make it less accurate. Stokvis changed the instrument's former name "Autotonograph," to "Tensograph."

In the same year Darrow [3] also used our device for psychological investigations and obtained good results.

In 1939 Doupe, Newman and Wilkins [11] used the same principle to record the systolic blood pressure, replacing the contact instrument for the transformation of the impulses into electric current by a mirrored tambour,

which deflected a light beam against a photocell; this measure was intended to avoid contact difficulties.

We utilized a similar system in 1935, but abandoned it, because it was not sufficiently selective for registration of the diastolic pressure.

Many investigators have published papers on the results obtained by the use of our original machine. Von Diringshofen [12] employed the machine in collaboration with the German Air Force to investigate pressure changes during power dives and tail spins under actual flying conditions. A copy of a record taken with the machine by him is shown in figure 11. Poeck [13] investigated the influence of evipal anesthesia on the blood pressure. Kronfeld, Mueller and Reiner [4] did extensive investigations of the influence of excitement and nervous unrest on the blood pressure. Groedel and McClellan [14] and Peemoeller and Lund [15] examined the behavior of the blood pressure during carbon dioxide baths. Reiner [16] studied the influence of cross examinations on the blood pressure of criminals; Fasshauer and Oettel [17] investigated the changes in blood pressure occurring during changes in posture on a tilting table; Von Bergmann [18] reported the influence of excitement on the blood pressure of thyreotoxic patients.

The use of a simple mechanical contact instrument was unsatisfactory for obtaining absolutely accurate readings of the diastolic pressure, although the systolic tracings conformed well with the values found with the Korotkov method. However, as always stressed, changes in magnitude of the spikes obtained while inflating a cuff are not a reliable sign of the diastolic pressure. No mechanical instrument can be used for the registration of the oscillations at the diastolic point, since the diastolic reading always would depend on the magnitude of the oscillations. Furthermore, the instrument is intended to test pilots under actual flight conditions. For this reason it must be entirely insensitive to sudden accelerations, a requirement which is never fulfilled by a mechanical contact instrument. It was, therefore, advisable to replace the original contact instrument and its later modification, the light beam-photo cell device, by a system of heated wires, whose electric conductivity was sensitive to air cooling.

The puffs, originating in the lower cuff, blow against one coil of a Wheatstone bridge, thus causing an imbalance. The bridge consists of four electrically heated coils of wire with a high temperature coefficient of resistance. Nickel was used for this purpose.

The current, which now flows from the unbalanced bridge, energizes a sensitive relay which activities a power relay which, in turn, directs the solenoid valve. The response of such a bolometer, as the heated wire bridge is technically called, depends only upon the speed of the air flow directed against its coils and not primarily upon the duration or magnitude of the air stream. In a series of experiments, which will be published in another paper, it was determined that the characteristic of the oscillometric curve for the diastolic blood pressure is a sudden change in steepness of the ascending branch of each wave at the moment when the arterial wall begins to

flutter. The same finding was made by Bazett, Laplace and Scott [19] in their investigation of the oscillometric criteria of the diastolic blood pressure. Since the bolometer is highly sensitive to changes in air speed, a point could easily be selected, by gradually shunting the sensitive relay, which would

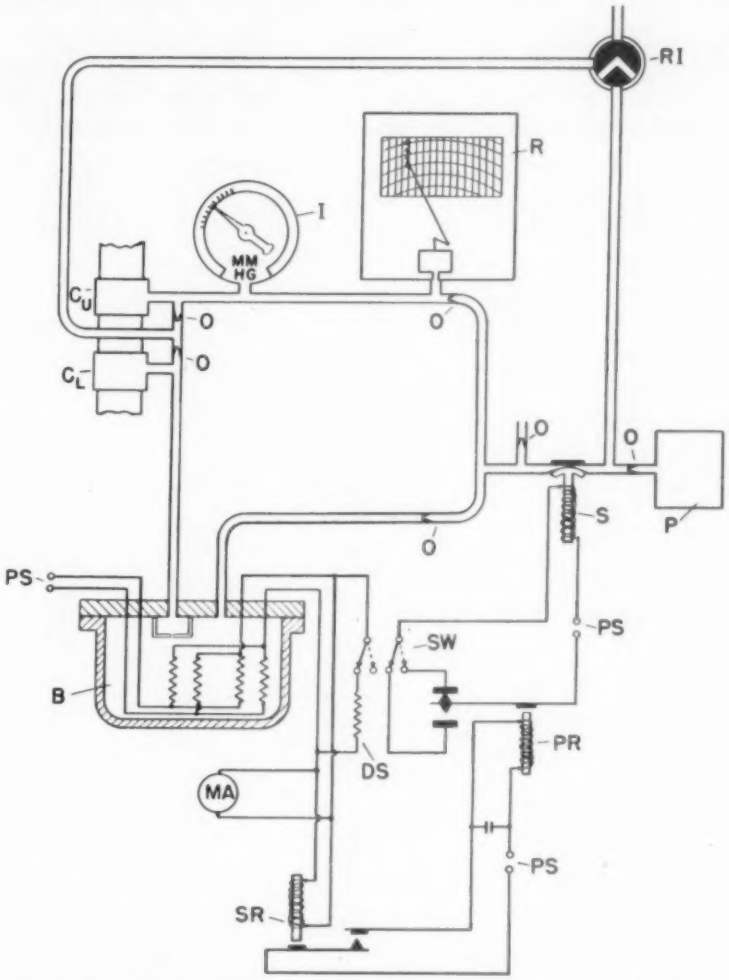

FIG. 2. Actual design of the sphygmotonograph. P = pump. O = orifices. S = solenoid pinching valve. I = indicating instrument. R = recorder. C_u = upper cuff. C_l = lower cuff. B = bolometer. SR = sensitive relay. PR = power relay. DS = diastolic shunt. SW = diast.-syst. switch. R.I. = pet cock for rapid inflation and deflation of the cuff.

correspond with the sudden change in steepness of the oscillometric curve occurring at the diastolic pressure.

This bolometer was placed in a chamber which was kept at the same pressure as both bags of the cuff, by using orifices in the air supply lines to the cuff and the bolometer chamber, which are proportional to their respective

sizes. By this arrangement (figure 2) only the puffs resulting from pulse oscillations against the lower cuff, which is on the same pressure level as the upper cuff, act against the bolometer, while all fluctuations of ascending or descending air pressure in the whole system do not influence the "pulse detector" at all. At the same time the two-bag system prevents the border beats from reaching the lower cuff.

In order to avoid a shock-like operation of the machine, a condenser is inserted across the contact of the sensitive relay. The condenser is charged by every contact which this relay makes. The size is such as to keep the

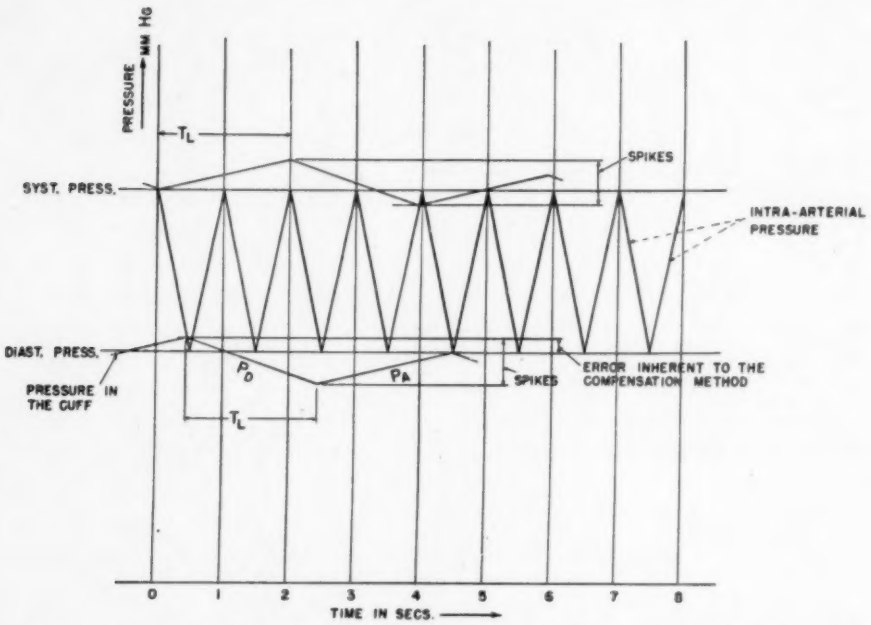

FIG. 3. Scheme of action of the sphygmotonograph. The interarterial fluctuations of the blood pressure are only sketched. t_l = duration of the time lag, p_d = speed of deflation of the cuff, p_a = speed of inflation of the cuff.

power relay closed and the pinching valve open or closed, depending on the position of the switch, for the time of two seconds after one impulse has occurred. If, in this period of two seconds, another contact occurs, a new time lag of two seconds is added. If not, the power relay breaks after two seconds, as explained in figure 3. The time lag of two seconds was chosen in order to bridge from one pulse to the next, even in cases of heart block with only 30 pulses per minute.

The pulse rate can be counted from the oscillations made by the pointer of the indicating instrument which is connected to the upper cuff and which, therefore, receives the oscillations of the border beats even when the systolic pressure is reached. When a diastolic reading is taken, the pulse rate can also be seen at the pointer of the milliammeter, which shows roughly the

currents coming from the bolometer. At the same time this instrument permits the resetting of the bolometer to zero if this point should have been lost. A variable resistor across one of the bolometer coils permits this resetting; however, this is very rarely necessary.

A small, built-in motor driven compressor provides the whole device with the necessary amount of compressed air. In order to make the instrument explosion proof for its use in the operating room, it was housed in a heavy metal casing. The compressor draws its air supply through a 12 foot tube. The electric cord also runs through this tube, distant from the field of explosive gases in the operating room. Rapid inflation of the cuff can be affected through a rapid inflating valve which connects the compressor directly to the cuff, avoiding the slow ascent through the orifices in case a rapid start for the tracing of the systolic pressure seems desirable. The same by-pass can be used in another position for rapid deflation of the cuffs after the examination is finished or when it is interrupted.

The device is very simple to use. The cuff is applied snugly and high up on the arm of the patient. The machine is connected to an electric outlet and the recorder pen filled with ink. The switch is then brought into position "diastolic" and within a few seconds the machine climbs to the diastolic pressure and remains there and follows it continuously. If a systolic reading is desired, the switch is then thrown over into the "systolic" position. The machine climbs to the systolic level and stays there continuously. When the examination is finished, the switch is brought back into the "off" position and the cuff empties automatically through the rapid deflation valve.

Measurements are carried out as follows:

Diastolic Blood Pressure. The electric switch is brought into the position "diastolic," thereby keeping the valve open as long as no sufficiently steep impulses hit the bolometer. The pressure in the cuffs and in the bolometer chamber climbs to the point at which the first sufficiently steep oscillation occurs. At this moment the valve closes and the pressure decreases. Because of the time lag, the valve is kept closed for two seconds, during which the pressure in the system falls, owing to the continuous leak. If no other impulse of the steepness for which the instrument has been set hits the bolometer in the meantime, the valve will open again after two seconds and permit compressed gas to reënter the bag-chamber system. The size of the spikes resulting from this type of operation is determined by four factors: the time lag (t_1); speed of inflation (p_a); speed of deflation (p_d); and finally, to a certain extent, by the pulse rate (t_p) (figure 3).

Systolic Blood Pressure. The switch is thrown from the diastolic to the systolic position, which means that now every puff on the bolometer opens the valve. Since in the region between systolic and diastolic pressure every pulse causes a puff, the valve is immediately opened and is kept open because of the time lag which bridges from one pulse to the next, unless the time interval from one impulse to the next is longer than two seconds. When

the pressure in the upper cuff has risen to a level just above the systolic pressure, no impulse can occur in the lower cuff, and after the time lag of two seconds, the valve closes. Air escapes through the leak until the first oscillation in the lower cuff recurs and causes the whole process to be repeated. The size of the spikes depends on the factors mentioned for the diastolic blood pressure.

The time lag of two seconds was chosen for reasons mentioned above. An inflation speed of 3 mm. Hg per second and a deflation speed of 3 mm. Hg per second were selected in order to comply as nearly as advisable with the recommendations of the American Heart Association for standardization of blood pressure readings. The size of a spike, for the diastolic as well as for the systolic pressure, caused by one single puff upon the bolometer, must therefore theoretically be 6 mm. Hg. From the manner of action described above, it is clear that the reading for the diastolic pressure is represented by the upper turning point of the diastolic spike, whereas the systolic pressure is represented by the lowest turning point of the systolic spike.

The rapidity with which readings are automatically taken by the machine can easily be deduced mathematically. After the first impulse has reached the bolometer, the time lag keeps the valve open for two seconds, during which the pressure increases 6 mm. After two seconds, the valve closes; the pressure has to fall for two more seconds in order to come back to the original level, where again a puff hits the bolometer. This means that every four seconds a reading is taken, or 15 readings per minute. If, in the meantime, the blood pressure has increased, the next reading will be taken by the machine after an interval of less than four seconds. If the blood pressure has decreased, the time interval will be longer than four seconds, depending on the amount of decrease.

It must be kept in mind that the compensation method in itself has an inherent error as demonstrated in figure 3. The descending or ascending pressure in the cuff does not always hit the pulse wave on its tip. This error depends on the speed of inflation and deflation and the pulse rate. The higher the inflation and deflation speed, the greater the error. The higher the pulse rate, the smaller the possible error. With the data standards chosen for the instrument, the maximal error at a pulse rate of 60 is 3 mm. Hg. An absolutely even blood pressure can, therefore, be recorded by an uneven tracing with maximal distortions of 3 mm. Hg. The same error can always distort the results of pressure measurements taken in the usual way, a factor important in making comparative readings.

Since the machine is limited in its inflation and deflation speed by choosing certain sizes of the inlet and outlet orifices, it is obvious that it cannot follow minute blood pressure changes which occur with a higher rapidity than the speed given by the inflation and deflation orifices. Hereby the regulation spikes gain the importance of indicating whether or not variations in blood pressure are followed by the machine minutely. If an ascending or descending branch of a tracing does not contain a spike at least every

two seconds, it means that the tracing is not as steep as the change in blood pressure and the machine is too inert to follow the original change with sufficient speed.

In order to prove that the machine in itself does not change its sensitivity, a container of about 1000 c.c. size was connected with one opening by a narrow orifice to the slit above the exposed coil of the bolometer. Another opening of the container was connected to the solenoid valve. The switch was then brought into the position "diastolic" and a tracing was obtained. The compressed gas entered through the open valve into the container,

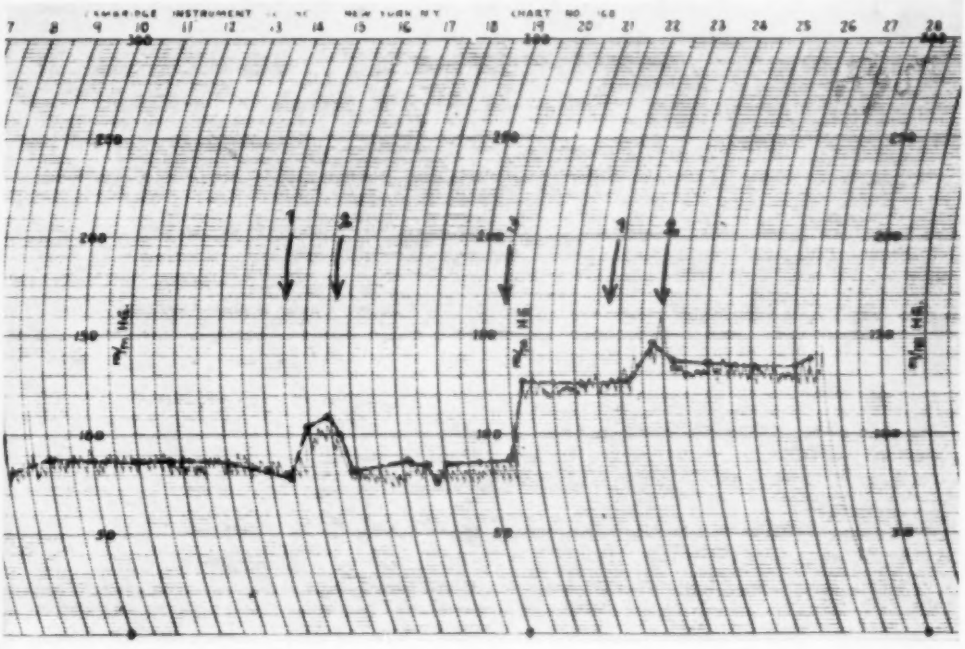

FIG. 4. Tracing of the diastolic and systolic pressure taken on both arms of a patient at the same time with two machines. Both records are later traced one over the other. At 1, a breath holding test is performed and ended at 2. At 3, the machine is switched from diastolic to systolic.

raising its pressure to a point where the speed of air directed against the bolometer was large enough to cause an impulse over the relays and to close the valve. The leak in the system now allowed the pressure to decrease for two seconds due to the time lag. After this time lag of two seconds was over, the valve reopened and the action began again. If the machine did not show any change in sensitivity, all the top points of the tracing must be at exactly the same level, while the spikes must be absolutely alike.

The diastolic adjustment was set to correspond with the values obtained by the auscultatory method. If the assumption was correct that there is a

definite characteristic change in steepness of the oscillogram at the point at which the auscultatory signs for the diastolic pressure appear, it should be possible to set the diastolic sensitivity in one case in accordance with the auscultatory finding, and this value should be correct in all other cases as well. As shown below, through comparative readings in a great number of patients, this was the case. At the same time, auscultatory controls for the diastolic pressure in one case with fluctuating blood pressure must correspond to the respective points in the sphygmotonogram. This, too, is true.

Since this sensitivity is electrically defined, we were able to create an adjustment device for the diastolic sensitivity based on electric and air flow conditions only. It is no longer necessary to adjust the machine to the patient, but the following data represent the sensitivity necessary to obtain good conformity. Air under a pressure of 50 mm. Hg, blown through a very narrow orifice of an exactly determined size against the exposed coil of the bolometer, must cause a current of 455 microamperes to flow to the relay. Since the relay itself is previously set exactly to "make" at a certain current, the diastolic sensitivity is electrically defined. If this definition is correct, one machine must not only give satisfactory conformity with an auscultatory reading in a great number of patients, but two machines attached to both arms of a patient with an equal pressure on both arms must give the same results and must show the same picture for fluctuations of the diastolic pressure. This is the case as shown in figure 4 in which the sphygmotonogram of two machines, used on the same patient, are traced, one over the other, and show a satisfactory identity.

II

It is obvious that there are certain physiological objections to the method itself. Taking long tracings of the systolic blood pressure causes a partial arrest of circulation in the arm, which is said to have detrimental effects on the nerve trunk, on the vessels, or on the muscles. After all, it must be remembered that no total arrest of the circulation takes place, since about every third pulse goes through. Thomas Lewis [20] in his book on "Vascular Disorders of the Limbs" proves that even total arrest in an arm up to half an hour does not cause any injury to the limb. From the many thousands of cases treated with Bier's hyperemia, it is known that even much longer periods of a high grade stagnation and pressure on the nerve trunk do not result in damage. The shortest period reported for a Volkmann contracture was five hours of total arrest *and* direct injury to the artery. We have so far examined more than 400 cases taking continuous systolic tracings for at least 10 minutes, but not more than 30 minutes without interruption. In none of these cases has any injury been observed, although some cases were examined for a period lasting from five to seven hours, records being taken for 20 minutes and the cuffs emptied for five minutes. After a period of about 10 minutes, numbness and a certain tickling sensation appear in the

fingers, which some patients call very uncomfortable, whereas others are not much disturbed by it. It is obvious that during anesthesia these questions are of no importance. In three of our cases we were compelled to stop the examination after a couple of minutes, since petechial bleeding appeared on the skin of the arm. These three patients had recovered from an infectious disease a short time before the test and had a positive Rumple-Leede phenomenon.

Another objection concerns the influence of the discomfort on the blood pressure itself. In order to test this, tracings of 15 minutes' duration in 10 unselected patients in a quiet ward were taken, so that no other psychic influence disturbed our patients. In none of them did the systolic blood pressure change more than $\pm$ 5 mm. Hg during the whole period of observation.

FIG. 5. The sphygmotonograph.

Another objection involves the question whether the stagnation of blood in one part of the circulatory system decreases the circulating blood volume so much that this in itself causes changes of the blood pressure. In none of the above-mentioned 10 patients did the systolic blood pressure taken by the auscultatory method immediately before the start of the sphygmotonogram vary more than $\pm$ 3 mm. Hg from the average blood pressure obtained during the 15 minutes of continuous recording.

In order to prove the accuracy of the device, 110 unselected male and female cases from the wards were examined in the following way:

All patients were resting in bed. The cuff of the machine (figure 5) was then applied high up and snugly on the upper arm of the patient and rapidly inflated through the special valve. The machine was then switched out and with a stethoscope a systolic and diastolic reading was taken in the usual manner. After the pressure of the cuff had come down to zero, a

diastolic and then a systolic reading was recorded by the machine, always taking the average of the second, third and fourth readings of the machine as the final result. Immediately thereafter another auscultatory reading, using the first mentioned technic, was made. The average results of the first and the second auscultatory reading were taken as a final auscultatory result. The auscultatory readings were made by the author with few exceptions, in which they were taken by other physicians. As criterion for the diastolic pressure, the end of the fourth phase was considered to be correct, a point to which the automatic diastolic recording of the machine was also adjusted.

Taking the average of 109 cases, the automatically recorded results for the systolic pressure were 0.06 mm. Hg higher than the auscultatory values found. In one case with a severe Moenckeberg sclerosis, neither the sphygmotonograph nor the auscultatory method gave a good result. In table 1 the number of cases with the different degrees of deviation are shown.

TABLE I

Deviations of Measurements Taken With the Sphygmotonograph from the Values Found by Auscultation

mm. Hg	Number of Cases			
	Systolic		Diastolic	
0	33		20	
	Minus	Plus	Minus	Plus
1–3	42	20	27	27
4–6	7	2	13	2
7–10		2		5
more than 10	2			3

For the diastolic pressure, the automatically recorded results taken from the average of 98 cases were 4.0 mm. Hg lower than the values found by auscultation. Table 1 shows the different degrees of deviation and the number of cases concerned. In 11 cases no satisfactory auscultatory readings could be obtained, and seven patients examined with the machine did not yield a satisfactory result.

In order to prove the accuracy of the machine, a microphone was placed over the brachial artery while the cuff of the machine was applied proximally. The power relay was then disconnected from the valve and connected in such a way as to close a small current through the string of an electrocardiograph when the relay pulled in. At the same time the microphone was connected to the sound recording unit of the same electrocardiograph. If the results of the sphygmotonograph are correct, the first closing

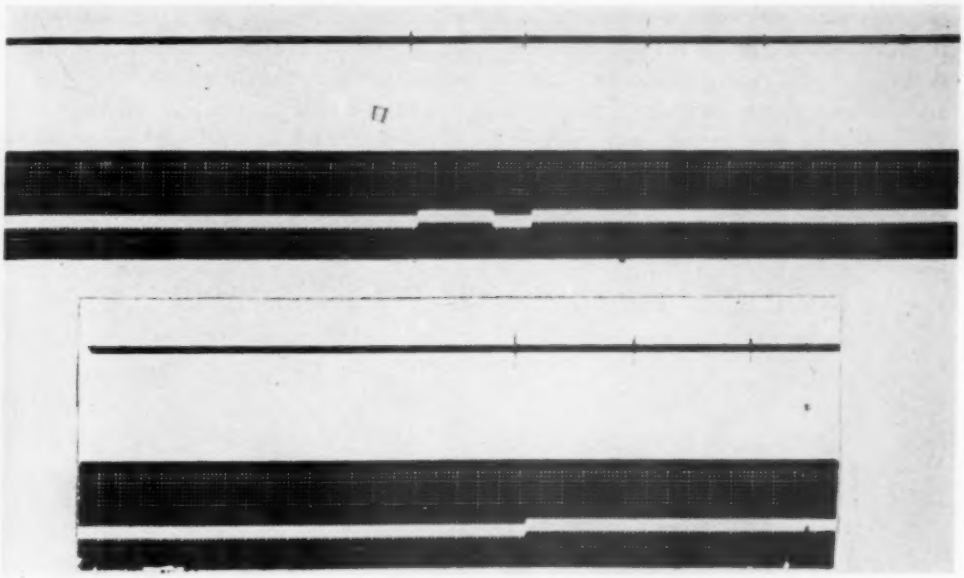

FIG. 6. Record confirming the accuracy of the measurements taken with the sphygmotonograph. The upper tracing is taken at the systolic level, the lower at the diastolic level. A microphone is placed over the brachial artery distal from the cuff of the sphygmotonograph. The contacts of the power relay close a current through the string of the electrocardiograph when the former is pulled in. The first sound in the systolic tracing as well as in the diastolic coincides with the first action of the machine.

FIG. 7. V. D., white male, aged 21. Tracing of the diastolic and systolic pressure showing Mayer-Traube-Hering waves in the systolic tracing which disappear under the influence of 0.02 gram morphine. At 1 injection of 0.02 morphine. At 2 the machine is switched from diastolic to systolic.

of the circuit over the galvanometer string should coincide with the first appearance of a sound, for the systolic with falling pressure as well as for the diastolic with rising pressure. Seven patients were examined in this way. In three of them no satisfactory sound tracings could be obtained owing to faintness of the sound, involuntary movements or generally unclear sound picture. In four patients the results were satisfactory. None of them showed a deviation of more than one beat between the stethogram and the sphygmotonogram. Such a tracing is shown in figure 6.

A discussion of the question of whether the sphygmotonographic results coincide with values found by intra-arterial measurements is purposely

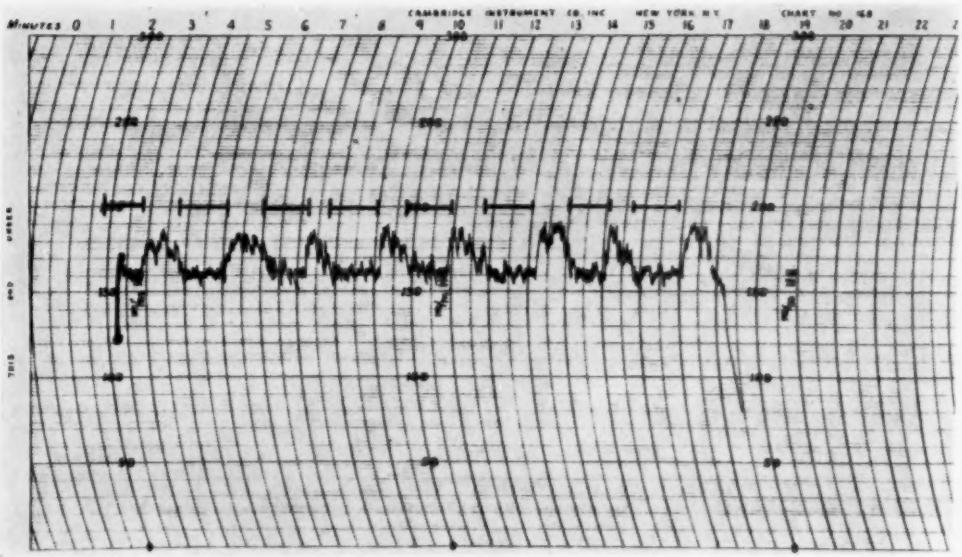

FIG. 8. L. H., white male, aged 68. The influence of Cheyne-Stokes breathing on the systolic blood pressure. The heavy lines above the tracing represent the periods of apnea, the pauses the periods of breathing.

avoided. Such comparative examinations are in the course of completion and will be reported later. The sphygmotonograph is set to give continuous readings of systolic and diastolic values as found with the auscultatory method when used accurately. This method gives the end pressure and not the side pressure, since it is an occlusive one.

A few basic facts found in most of the tracings seem worth mentioning at this point. In many persons the blood pressure does not run evenly. In many patients examined, we found Mayer-Traube-Hering waves between 15 and 30 seconds long and between 4 and 12 mm. Hg in height. These waves, as shown in figure 7, seem largely influenced by psychic emotions and very often disappear under ordinary doses of morphine. When they disappear during anesthesia, it points to the fact that the anesthesia is unduly deep, causing loss of normal circulatory reactions. They

seem to be lost in patients with excessive hypertension and to disappear in shock. They seem to be more pronounced when there is a slight increase of carbon dioxide in the arterial blood when breathing is impaired as, for example, in laryngospasm. Stress must be put upon the fact that even very

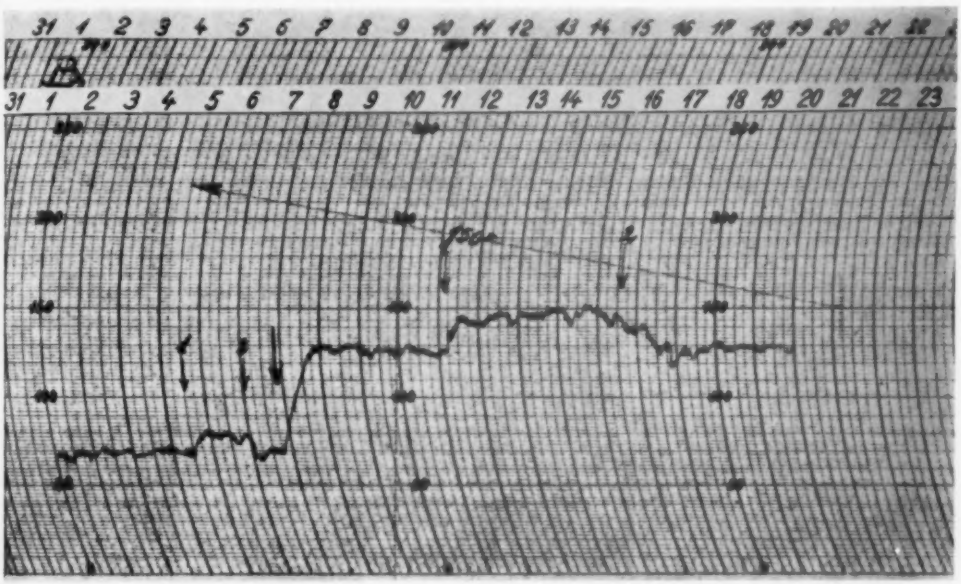

FIG. 9. A. K., white male, aged 22. The influence of a conversation on the diastolic and systolic blood pressure of a thyreotoxic man. Conversation begins at 1 and ends at 2.

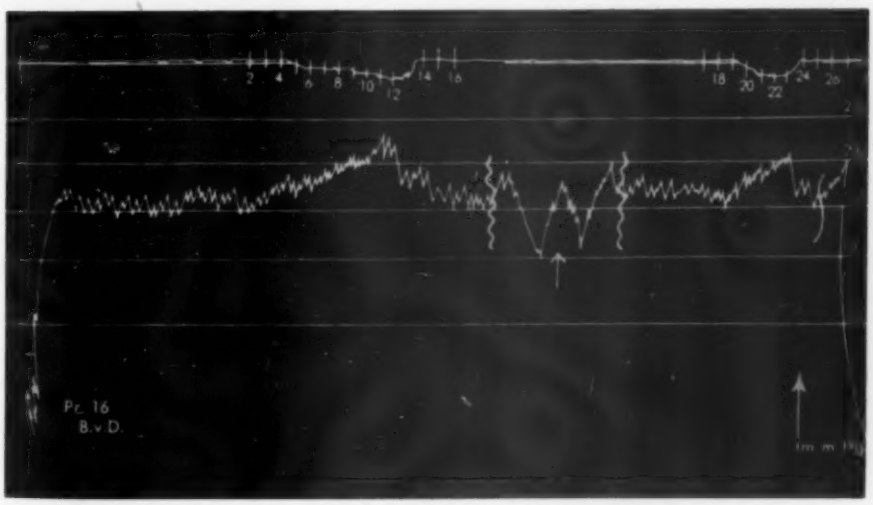

FIG. 10. Systolic blood pressure of a pilot in an airplane during a tail spin with increasing centrifugal acceleration up to 4.5 g (From H. v. Diringshofen [12]). The degree of acceleration is shown by the deviation from the horizontal of the upper marker line. (Marks 10 seconds.)

slight excitement can cause considerable increase in blood pressure; mere conversation or watching the blood pressure machine can cause increases up to 15 mm. Hg in normal persons. Such increases are much more outspoken in thyreotoxic patients and in patients with slight hypertension and suggest, when present in patients with otherwise normal blood pressure, a tendency towards hypertension.

In general it can be said that to obtain basic blood pressure conditions as represented by a steady non-fluctuating sphygmotonogram, it is necessary to have the patient at absolute rest with no disturbances whatsoever (figure 9).

We believe that this instrument in its various applications as shown in figures 8 and 10 can essentially clarify many conditions now obscure, and prevent unpleasant incidents during anesthesia.

Summary

1. A machine is described which automatically takes continuous records of the systolic as well as diastolic blood pressure of man.

The principle and the detailed construction are shown and the mechanical arrangements and working conditions discussed. The inertia of the machine is shown and the meaning of the obtained tracings is discussed.

2. A simple mechanical contact device is not satisfactory for registering the diastolic pressure, since it is dependent on the magnitude of the oscillations instead of on the steepness of the ascending branch. A heated wire system (bolometer) is used to transform the puffs of air into electric currents.

3. The steepness of the ascending branch of the diastolic oscillation is an exact criterion for the diastolic pressure.

4. The accuracy of the sphygmotonograph was proved by comparisons with the auscultatory method in 109 patients. The average difference for the systolic pressure was 0.06 mm. Hg, for the diastolic pressure 4.0 mm. Hg.

5. Records taken from both arms of the same patient with two machines are identical.

6. Taking uninterrupted records for a period of 30 minutes with partial arrest of the circulation in the limb concerned does not produce any detrimental effect on the vessels, nerves or muscles.

7. The partial arrest of circulation and the pressure on the limb do not produce changes in the blood pressure.

8. Comparative measurements with the Korotkov method, using a recording microphone instead of the stethoscope, show the accuracy of the sphygmotonograph.

9. Many normal persons show Mayer-Traube-Hering waves of a wave length of about 30 seconds and a height up to 12 mm. Hg in size under excitement and impaired breathing conditions.

10. Even slight mental work or excitement may cause a considerable in-

crease in diastolic and systolic blood pressure, especially in individuals in the very beginning of hypertension.

I wish to express my thanks to the engineering staff of the Cambridge Instrument Co. for their assistance in planning many technical details.

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CASE REPORTS

LARYNGEAL AND SYSTEMIC HISTOPLASMOSIS (DARLING) *

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Medical interest in histoplasmosis (Darling) has been aroused recently by the increased number of reports published. These accounts indicate that this endemic disease has become more prevalent or that it has existed unrecognized. The difficulties encountered in clinical diagnosis of the disease are due apparently to the variety of symptoms presented by these patients. The specific organism has been isolated by cultures in only a few patients during life or from tissues post mortem. There is no information concerning the morbidity of the disease because all patients known to have had the infection have died. Little is known about the predisposing factors of the infection. Heredity and environment seem to have no effect on the course. The disease, though endemic, is not restricted in geographic distribution. Twenty-two males and 10 females have died; their age incidence ranges from six months to 69 years. The course of the disease seems to be short in the very young and longer in older persons and is unaffected by climate, season, or state of hygiene. Occupation seems not to be a factor, although many of the patients lived in rural districts or had close contact with farm products.

The causal organism is *Histoplasma capsulatum*, a member of the fungi imperfecti. It exists in yeast and mycelial forms. The yeast form is pathogenic in man although the mycelial form was found once in human tissues.[1] The hyphae are 2.5 to 11.5 μ in diameter and may be either straight, branched, or septate. Chlamydospores range from 4 to 10 μ in diameter and are rich in fat. They are sessile, lateral, intercalary, or pedicellate. The characteristic ascus-like bodies are 10 to 25 μ in diameter, rich in fat, and must be present for identification of the fungus organism. At first they are smooth or crenate but become spinose with barbs as long as 5 to 6 μ. They are attached to hyphae terminally, laterally, or in the interstices.[2] The fungus grows well on various media and the disease can be reproduced in animals. The mode of infection, distribution outside the body, and the nature of immunity, if any, are unknown.

The organism, once established in the body, invades many tissues. There has been enlargement of the liver or spleen with or without tubercle-like nodules in most of the cases; small, hemorrhagic, firm, white nodules or patchy consolidation of the lungs in 50 per cent; focal necrosis in cervical, axillary, tracheobronchial, mesenteric and periaortic lymph nodes in many; necrosis, hemorrhage

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or enlargement of the suprarenal glands in 10; multiple ulcerations, scaling, nodular thickenings, or purpuric spots in the skin of six; granulomatous lesions of the epiglottis, vocal cords, and larynx in two; small gray nodules on the serosa of the duodenum, ileum and colon; granular annular ulcers of the jejunum, ileum, and colon; longitudinal ulcers of the colon and rectum; small gray nodules on the anterior surface of the left ventricle of the heart, meninges, thymus, and pancreas; and small hemorrhages in the kidney.

Microscopic findings vary as widely as the gross pathological changes. Coccoid bodies corresponding to the yeast form of *Histoplasma capsulatum* have been described in alveolar cells; in monocytic phagocytes of alveolar and bronchial exudates, nasal, buccal, palatine, or laryngeal ulcers, skin, epicardium, meninges, duodenal serosa, intestinal lamina propria, periportal regions of the liver, necrotic regions in the spleen, lymph nodes, renal medulla and glomerular tufts, sternal bone marrow and ear exudates; in endothelial cells of the capillaries, liver, spleen, lymph nodes, and skin; in medullary and cortical cells of the suprarenal gland; in the epithelium of the skin; and in the acinar epithelium of the prostate.

Accompanying these parasitized cells are lymphocytic exudates with or without necrosis, scar tissue, or hyaline masses. Giant cells were reported once in the spleen. The lesions resemble tuberculosis. Watson [3] stated that the first change following parasitism of the cells is necrosis and lymphocytic exudates, followed by scarring and hyalinization. In ulcers, lymphocytes are numerous, and there are very few polynuclear leukocytes. Phagocytized mononuclear cells are abundant. In the lung a lymphocytic bronchopneumonia may develop. The mycelial form of the organism has been seen in the bronchial exudate of one patient.[1]

The invaded cells may have only four or five coccoid bodies or 50 or more. These bodies are 2 to 4 μ in diameter with central dark blue granules and pale pink cytoplasm, in hematoxylin and eosin-stained preparations. A narrow refractile zone surrounds the cell. The granules may be single or five to six in number. They sometimes form chains or crescents within the organism that suggest the merozoites of protozoan parasites. At times the cytoplasm appears vacuolated.

Darling [4] listed the syndrome of anemia, fever, splenomegaly, and weight loss as characteristic of the disease. Symptoms referable to the respiratory tract were cough, rhinitis, rhinorrhagia, sore throat, hoarseness, and dyspnea. Gastrointestinal symptoms were sore gums, ulcers of the mouth or tongue, nausea, emesis, epigastric fullness, diarrhea with or without blood, and loss of weight. The liver, spleen, or lymph nodes may or may not be enlarged. Low-grade fever reported in many patients markedly simulates the afternoon or early evening fever of tuberculosis. Blood conditions vary. Five cases had a chronic otitis media. Ulcers, purpura, bullae, scaling, jaundice and brown pigmentation of the skin have been described.

Various agents have been tried in an attempt to halt the progress of the disease. Among them are quinine, potassium iodide, neoarsphenamine, bismuth subnitrate, stovarsol, ionized copper, roentgen-ray, splenectomy, sulfanilamide, pentnucleotide, blood transfusions, potassium arsenite and tartar emetic. Meleney [5] suggested the use of antimony and potassium compounds.

Only fatal infections thus far have been recorded. Some patients seem to die from a pneumonia, others from "heart failure." Lesions of the suprarenal glands have been reported in 10; death in these may have been due to suprarenal insufficiency.

Histoplasmosis may be diagnosed in various ways. Stains of the peripheral blood and of bone marrow biopsies may afford a clue. Biopsies of available tissues, such as laryngeal, buccal, or rectal ulcers, may furnish histological and cultural evidence of the condition. Dextrose broth culture filtrates of the fungus isolated from lesions produce specific immediate and delayed skin reactions.[8] An immediate reaction, like an urticarial wheal 1 to 1.5 cm. in diameter, appears with undiluted filtrate in 15 to 30 minutes after the injection. The delayed reaction, clearly visible after 18 to 24 hours, consists of a marked erythema and swelling of the skin which gradually disappears after five or six days. Dextrose broth filtrates treated with three volumes of acetone yield the specific substance responsible for the skin reaction. This flocculent precipitate, when redissolved in saline and injected intradermally, produces a typical erythematous wheal in 30 to 60 minutes.

Case Report

A 63-year-old Latvian bartender had an irritation of his throat and increasing hoarseness for 18 months. He had lost 40 pounds in weight in six months and for one month had difficulty in swallowing. He noticed increasing weakness and a chronic cough, productive of a thin, watery sputum. His appetite was poor, and he had a sensation of epigastric fullness aggravated by food but relieved by emesis, soda and warm water. He had impaired hearing in his left ear since childhood, associated with an occasional thick yellow exudate. In 1915, he had diphtheria; in 1932, pleurisy. Syphilis and gonorrhea, contracted in 1925, had been adequately treated.

On admission to the hospital the patient appeared to have lost weight. His blood pressure was 115 mm. Hg systolic and 75 mm. diastolic, pulse 80, and temperature 98.6° F. The lips and buccal mucosa were pale. The gums were soft and had receded. Hearing in his left ear was markedly impaired. The chest was emphysematous and the lungs hyperresonant but without adventitious sounds. The abdomen was protuberant and the liver palpable three fingers' breadth below the costal margin. There was wasting of the muscles of the extremities and coarse thickening and longitudinal ridging of the finger and toe nails. Mirror examination of the larynx revealed a small polypoid tumor in the midportion of the phonating edge of the left true cord. The aryepiglottic folds and arytenoids were thickened and their laryngeal surfaces had a soft, slightly ulcerated mass extending across the entire posterior commissure. The lesion was red and covered with a gray exudate. The motility of the cords was impaired. Physical examination was otherwise normal. The Kahn test was negative, the urine was normal, and repeated stool and sputum examinations were negative. Sternal biopsies and differential blood stains were normal. The red blood cells ranged between 5,120,000 on admission to 4,680,000 shortly before death; the hemoglobin was 15.4 to 12.8 grams per cent, and the leukocytes 7,950 to 5,620 per cu. mm. Roentgen examination of the larynx suggested an irregularity of the body of the thyroid cartilage and a slight increase in density about the arytenoids. The lungs had increased hilar shadows and calcified nodules in the left hilum, and the peribronchial markings were increased. A gastrointestinal study demonstrated only a decreased motility of the ileum. The liver and spleen were enlarged. Direct examination of the larynx substantiated the findings of mirror examination. A verrucous mass extended across the posterior commissure, spread

laterally into the ventricles and superiorly to involve the posterior portions of the false cords. The polyp on the left true cord as well as tissue from the posterior commissure was removed. The tissues were diagnosed as histoplasmosis of the larynx by Dr. Edwin F. Hirsch. Other tissues were removed two weeks later for further histological study and bacteriological culture. *Histoplasma capsulatum* was isolated from them on various mediums. The patient was discharged from the hospital and, until his last admission two months later, lost 80 pounds in weight, became progressively weaker, and developed a bronze pigmentation of the skin. As nutrition seemed of prime importance, treatment was so directed. Small ulcers appeared in the

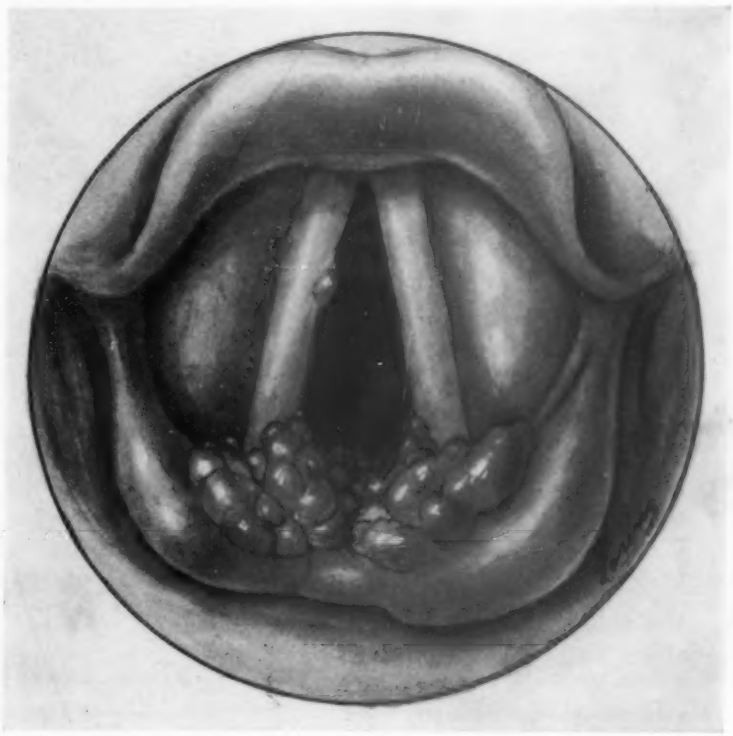

FIG. 1. Drawing illustrating the location and extent of the histoplasma granulation tissue lesions of the larynx.

left premolar region and on the right side of the base of the tongue from which no unusual organisms were cultured. He had late afternoon or early evening rises in temperature to 100° F. The constituents of the blood were within normal ranges. Neoarsphenamine, sulfanilamide, potassium iodide, yellow bone marrow and potassium permanganate gargles did not improve his general condition. The ulcers of the mouth and tongue healed. The laryngeal lesion improved. During one month he received 280 grains of tartar emetic intravenously and by mouth, but without improvement generally. The patient died approximately five months after the diagnosis of histoplasmosis had been made.

Autopsy was done eight hours after death. The body weighed 100 pounds. There was poor oral hygiene with a blue-black discoloration of the gingival margins and caries of the teeth. The skin was generally pigmented light brown. Emaciation

was marked. The toe and finger nails were thickened and had prominent longitudinal ridges. The axillary, periaortic, abdominal, tracheobronchial, cervical, inguinal and biliary lymph nodes were not enlarged but the centers of some were yellow and slightly soft. Along the root of the mesentery were small, glistening, white nodules not larger than 3 mm. in diameter. Dense fibrous adhesions were between the lateral chest wall and the right lung. There was a moderate atherosclerosis of the aorta. The esophagus had slight epitheliosis and a small diverticulum. The heart had only a moderate cloudy swelling. It weighed 250 grams. The right suprarenal gland weighed 14.2 grams, had a firm fibrous capsule, and its center was caseous, gray-yellow

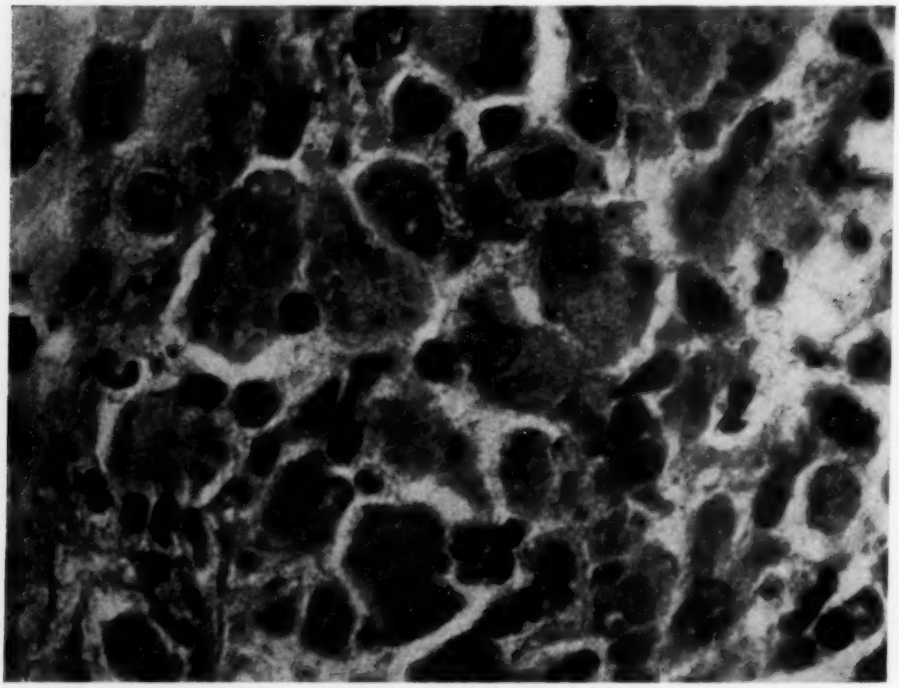

FIG. 2. Photomicrograph illustrating the large phagocytes with the histoplasma inclusions in the laryngeal granulation tissues. Hematoxylin-eosin stain × 980.

tissue. The similar left suprarenal gland weighed 14.5 grams. No normal suprarenal tissue remained. Each kidney weighed 200 grams and had slight senile nephrosclerosis. There were no changes of the gall-bladder and bile ducts, pancreas and pancreatic ducts. The pancreas weighed 86 grams. The liver had a moderate chronic passive hyperemia and weighed 1890 grams. The spleen weighed 475 grams and had only scattered gray-white nodules 2 to 4 mm. in diameter. The left lung weighed 595 grams; the right, 900 grams. They had only fibrous adhesions covering the pleura of the right lung. The stomach, duodenum, ileum, colon, and rectum were normal. The mucosa of the jejunum was hyperemic. Scattered regions with blebs seemed to contain gas and were on both the mesenteric and antimesenteric sides. These ranged from 3 mm. to 3.2 cm. in diameter. The larger regions seemed multiloculated and were raised as much as 1 cm. above the surrounding mucosa.

The vocal cords and larynx were hyperemic. In the right posterior commissure was a finely granular, gray-white tissue 0.6 by 0.2 cm. with several depressions 2 to 3

mm. deep. The vocal cords were smooth. In the right pyriform sinus were five gray-white nodules, 4 mm. in diameter. Another nodule was on the right posterior pillar. The left pyriform sinus had 11 similar nodules, three of which were confluent and shaped like a clover-leaf. Three other nodules were on the left posterior pillar. The base of the tongue had similar nodules. The tonsils were atrophied. The left middle ear was fibrous and hyperemic. The surrounding bone was soft and porous. The ear drum was perforated, thick, and gray. The external canal was filled with waxy material. A circular depression, 3.8 by 3.2 cm., of the frontal bone in the midline apparently was an old injury. The calvarium, dura, brain, dural sinuses, cerebrospinal

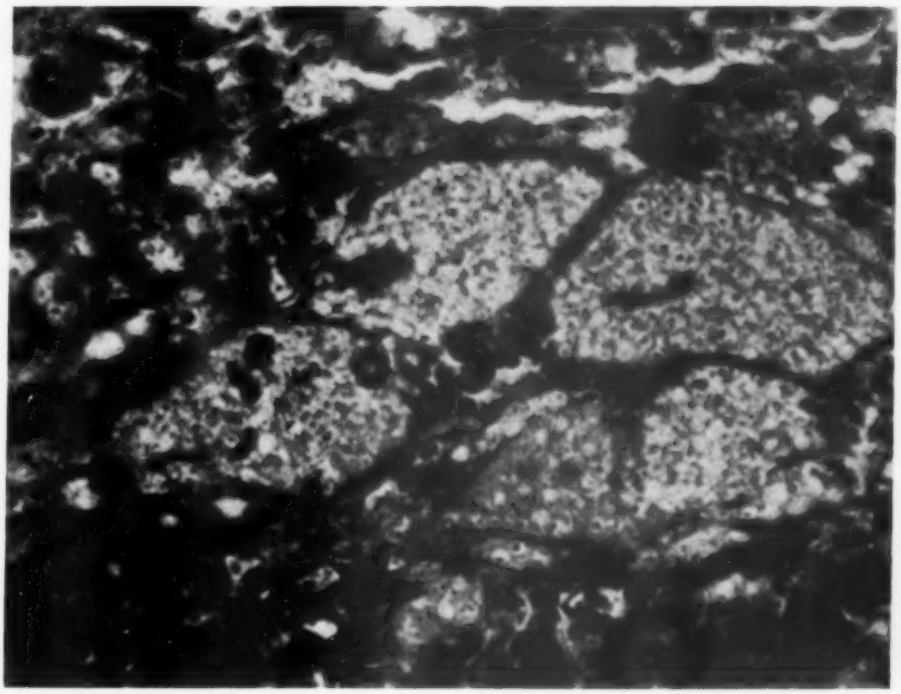

FIG. 3. Photomicrograph illustrating the parasitic invasion of swollen cortical cells of the suprarenal gland. Phosphotungstic acid-hematoxylin stain × 920.

fluid, hypophysis, accessory nasal sinuses, right middle ear, right and left mastoid processes, were without change.

Cultures of heart blood, cerebrospinal fluid, right and left suprarenal glands, pericardial fluid, and left ear exudates on Endo's agar, blood agar, dextrose agar, beef heart broth and dextrose broth were overgrown by *B. mucosus capsulatus*, and continued to be when subcultured twice, a week apart. *Histoplasma capsulatum* was not recovered from these cultures after three weeks.

Lymph nodes from various places were similar in histological detail. They were moderately edematous. In the cytoplasm of monocytic macrophages were spherical refractile bodies 2 to 4 μ in diameter. In the centers of these bodies were one to five dark blue granules; outside was a clear halo. There was a thin refractile capsule. Some of these bodies were extracellular. There were many large and small fibrous scars. With high magnification the centers of these scars consisted of disintegrating nuclei of monocytic cells and many pale oval bodies 2 to 4 μ in diameter without

basophilic granules. Outside of these regions in the larger scars was a zone of lymphocytes resembling a tubercle. An occasional multinucleated giant cell was found in some of the lymph nodes. Some of the parasitized cells had one or two oval bodies; others had 30 to 50. Sections stained by the Ziehl-Neelson method revealed no acid-fast organisms. Parasitized cells were also found in the sinuses. In a few places where the capillary endothelium was thickened, a parasitized endothelial cell was seen. In phosphotungstic acid-hematoxylin preparations the granules were dark blue and the clear zone faintly orange. In eosin-methylene blue preparations the granules were bright blue and the clear zone faintly pink. In preparations stained by Masson's trichrome method, the granules were brown to black and the clear zone was faintly green. These staining reactions correspond to those of collagen. The tracheobronchial lymph nodes contained monocytic phagocytes with carbon pigment and yeast bodies in their cytoplasm.

Tissues from the left middle ear were chronic granulation tissues with many mononuclear cells filled with the characteristic oval histoplasma organisms. Bone marrow sections showed the trabecular spaces filled with lymphocytes and mononuclear cells, singly or in clumps, containing parasites 2 to 4 μ in diameter.

Extensive portions of the histological preparations of the left and right suprarenal glands were necrotic. Radiating from the fibrous capsule into the granular debris were stalks of poorly vascular chronic granulation tissue. The necrotic portions were tissue debris with polynuclear leukocytes, lymphocytes, and mononuclear phagocytes. Much of the tissue debris with high magnification consisted of disintegrating masses of yeast bodies. At one place next to the fibrous tissue capsule were a few large cortical cells in parallel rows. The cytoplasm of these cells was filled with yeast bodies. Sections stained by the Ziehl-Neelson method failed to reveal acid-fast organisms. Some of the necrotic tissues were surrounded by zones of lymphocytes and a few large multinucleated giant cells.

The tissues of the larynx had a narrow regular surface squamous epithelium. The stroma was dense fibrous tissue with small foci of lymphocytes and monocytes. There were numerous mucous glands. In the cytoplasm of these gland cells were many parasites. They were demonstrated clearly in sections stained by hematoxylin and mucicarmine. The mucin stained bright pink, the vesicular nuclei had dark blue chromatin granules and in the cytoplasm both basally and toward the lumen were dark blue bodies 2 to 4 micra in diameter surrounded by a refractile halo. These corresponded to the parasites in other sections. Tissues of the pyriform sinuses had a narrow surface squamous epithelium resting on a dense fibrous tissue stroma containing many mucous and serous gland acini. In the fibrous tissue stroma were foci of lymphocytes and monocytes with parasitized cytoplasm. The cytoplasm of the mucous secreting cells was also parasitized. This was demonstrated best by hematoxylin and mucicarmine stains.

The mucosa of the jejunum was autolyzed. After a careful search only a few mononuclear cells were found at the tips of the villi, containing a few parasites. The submucosa was separated from the lamina propria and muscularis mucosa by a clear space but otherwise the jejunum was normal. Sections of the ribs, sternum, and vertebrae had only a few monocytic cells with cytoplasm containing parasites. In the muscle tissues about a rib was an encysted trichina larva. Scattered in the red pulp and Malpighian corpuscles of the spleen were large, single, and clumped parasitized mononuclear cells. There were also small fibrous scars with many parasitized monocytic cells. The liver had a chronic passive hyperemia. The fibrous connective tissue about the portal canals was increased and had many lymphocytes and large parasitized mononuclear cells. The adjacent liver cells also were parasitized. Some of the liver cells detached from the cords and in the connective tissues had many parasites. The gallbladder, pancreas, myocardium, and kidney tissues had no unusual changes. The

pleura of the lungs was thickened by fibrous tissues. The alveoli had fibrin, red blood cells, lymphocytes, and many monocytic phagocytes containing carbon pigment, blood pigment, or parasites. A few parasitized cells were in the alveolar septa. Along the endothelial edge of the capillaries were a few clusters of swollen parasitized mononuclear cells. Bronchial exudates also contained parasitized cells and small fibrous scars had the yeast-like organisms and vacuolated multinucleated giant cells. The lymphoid tissues along the interlobular septa of the thyroid had a few parasitized mononuclear cells. These cells were found also elsewhere. The testes had no changes except a few small collections of lymphocytes and large parasitized mononuclear cells beneath the tunica albuginea. A few parasitized cells were found in the acinar epithelium and lumina of the prostate. Histological preparations of the brain, hypophysis and Gasserian ganglion were without noteworthy changes.

Cultural Studies

Tissues and exudates removed from the larynx five months before death were cultured on various media at 37° C. and at room temperature. Growth was obtained easily after three to five days. Subcultures were made many times and the organism continued to grow, predominantly in the mycelial form. Various cultural studies of this and of material obtained from animals inoculated with the initial growth have been reported.[8]

The fungus grows on decaying material of many kinds, in sunlight and in the dark. Its growth is more abundant in the dark and more so in moist material. It is a fairly resistant organism but is killed in the autoclave in one hour at 15 pounds pressure or when subjected to freezing for one-half hour. When dextrose broth cultures were treated with various chemical agents in strength up to 10 per cent, the organism was very resistant to common acids, alkalies and sulfanilamide derivatives. There was no resistance to thymol, potassium permanganate, or tartar emetic.

Animal Studies

Fifteen white mice were injected intraperitoneally with 2 to 3 c.c. of a heavy suspension of the mycelial form of *Histoplasma capsulatum*. Two died; the rest were killed at intervals of one to six weeks. At autopsy nine had no gross pathological changes. One mouse had an abscess of the groin from which the fungus was recovered. Five mice had enlargement of the liver and spleen, but only one had minute gray nodules in the liver and spleen after three weeks. In two mice the mesenteric lymph nodes were enlarged. The fungus was recovered from either the liver, spleen, or lungs of all but four mice. Characteristic histological changes were found in the liver and spleen of all 15 and in the lungs of nine mice. Ten gave delayed positive skin reactions when 0.1 c.c. of a 1:100 dilution of dextrose broth filtrates of the fungus was injected intradermally. Five mice tested gave immediate positive reactions when 0.1 c.c. of an acetone precipitate of dextrose broth culture redissolved in saline was injected intradermally. Fifteen uninoculated mice gave negative results when tested for skin reactions.

Yeast forms of the fungus, 2 to 4 μ in diameter, were recovered from four of the mice. On subculture these changed to the mycelial form. Large yeast forms corresponding to those described by Moore[6] were recovered from one of the mice. On subculture smaller yeast forms developed and soon changed to

the mycelial form. Other mice inoculated with these large forms showed characteristic histological findings for *H. capsulatum.* Cultures of spleen and liver of these mice produced the mycelial form with characteristic chlamydospores.

Rats inoculated intraperitoneally with the mycelial form consistently failed to show any gross, histological, or cultural characteristics of the disease. Skin tests were negative.

Guinea pigs inoculated intraperitoneally gave variable results. No gross characteristic changes were evident. Histological evidence of the disease was found in the spleen and lymph nodes of only two guinea pigs. Positive cultures were obtained from the liver of one and the spleen of both of these guinea pigs but cultures of other animals were negative. One-tenth c.c. of a 1 : 10 dilution of histoplasma dextrose broth filtrate gave positive skin tests in only these two guinea pigs.

Rabbits inoculated intraperitoneally, intracerebrally, intravenously, intrapleurally and by gavage consistently gave negative gross, histological, cultural and skin test results. Eight mice, each fed 1 c.c. of a histoplasma suspension 10 times over a period of two weeks, also gave completely negative results.

Discussion

So that this disease may be fully understood and a cure effected, the fact should be recognized that it simulates many other clinical syndromes, especially tuberculosis. Not only are the clinical symptoms similar to tuberculosis but also the gross and microscopic pathological changes. Our case and that of Brown, Havens and Magath [7] had symptoms suggesting laryngeal tuberculosis or a tumor. Suprarenal insufficiency probably was the cause of death in our patient. Part of the classical syndrome of Addison's disease was present, but the blood chlorides were normal and the blood pressure was not lowered.

The remarkable feature histologically is the parasitic invasion of the cells in the suprarenal cortex. The fungus does not affect only the reticuloendothelial system but also invades epithelial cells. Similar parasitic invasion of the epithelial cells in the liver and in mucous and serous glands of the laryngeal tissues was also observed.

Summary

The clinical course and postmortem findings of a patient with laryngeal histoplasmosis is described. Although the symptoms caused by the fungus infection of the larynx were the patient's chief complaint, intracellular parasitism and destruction of the suprarenal glands by the disease caused an Addison's syndrome. Intracellular involvement of liver tissues and mucus secreting glands was observed. Broth culture filtrates of the fungus isolated from laryngeal lesions produced specific immediate and delayed skin reactions in the patient and in animals experimentally infected. The specific substance responsible for the skin reactions was precipitated with acetone and was readily soluble in saline solutions.

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SYPHILIS OF THE STOMACH: A CASE REPORT*

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The occurrence of gastric syphilis has been so well established that further proof of its existence is, in our opinion, not needed.[1-31] The instructive case herein reported is of interest because the classical pathologic criteria are so well fulfilled and because the diagnostic difficulties are well illustrated.

Case Report

The patient, a male 36 years of age, was admitted to the University clinics on November 26, 1940, complaining of anorexia, bloating, distention, abdominal distress, nausea, vomiting and loss of weight. He had been perfectly well until January 1940, when he began to notice a continuing lack of appetite. On May 5 he experienced nausea and vomited food following the noon meal. This recurred for five successive days and then disappeared. Abdominal bloating, distention and discomfort persisted and were not improved by a month's vacation in July. In August a gnawing epigastric "hunger pain" appeared, coming on about 11:30 a.m., 4 p.m., and 4:30 a.m., and lasting 15 to 20 minutes unless food or soda was taken, in which case prompt and complete relief was obtained. Occasionally nausea appeared in the midafternoon and usually led to emesis unless relieved by food. In the six months prior to admission the patient had lost 25 pounds in weight. The additional history was essentially irrelevant except for the statement that at the age of 17, following coitus with an infected person, the patient had developed a "pimple" on the dorsal shaft of the penis, over which a crust had formed with healing in four weeks. Apparently syphilis had not been suspected and hence no treatment had been instituted. Physical examination in November 1940 disclosed no significant abnormality except a scar on the left dorsum of the shaft of the penis. The neurologic examination was normal. The blood Wassermann and Kahn tests were both strongly positive (four plus) on two occasions. The spinal fluid Wassermann test was negative; the cell count was 6, Pandy negative, the pressure normal, the colloidal gold curve normal. The red blood cell

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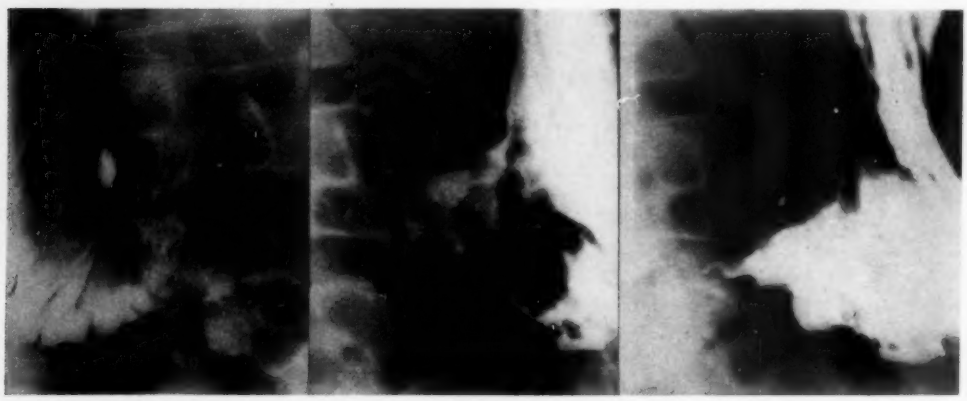
From the Frank Billings Medical Clinic, the Department of Medicine, University of Chicago.

count was 5.06 million, hemoglobin 92 per cent (Dare), white cell count 7600. Repeated urinalyses were normal. Three histamine tests of gastric secretion, using 0.6 to 0.8 mg. of histamine hydrochloride, disclosed a maximum free acidity of 25, 10, and 0 clinical units respectively. Examination of the feces for occult blood while the patient was on a meat free diet gave results varying from a negative to a strongly positive reaction.

The roentgenologic examination of the stomach on November 28 was reported by the examiner, Dr. Paul C. Hodges, in part as follows (see figure 1):



(*a*) (*b*) (*c*)

FIG. 1. Roentgenologic appearance of infiltrative ulcerative syphilis of the antrum of the stomach. (*a*) Taken with compression applied to the antrum, shows the collection of barium described on the greater curvature side of the antrum and the dilated second portion of the duodenum. (*b*) is another view of the antrum and the lower body of the stomach with compression, and (*c*) a view without compression. In (*b*) nodules outlined by thin layers of barium completely replace the normal rugal pattern in the distal portion of the antrum. In the proximal portion, the nodules of the anterior wall are superimposed on the normal appearing folds of the posterior wall. One of the folds, extending across the antrum from the lesser curvature, divides above and partially overlaps a large mass lying near the greater curvature. The collection of barium along the lesser curvature, distal to the angle, is presumably barium caught between folds. In (*c*) the irregular narrowing of the antrum caused by the thickening of the walls and the encroachment of the nodules on the lumen is more marked in the distal end where the lesion completely surrounds the lumen.

"There is a frank lesion of some sort in the pyloric antrum which I think almost certainly is a gastric ulcer at the greater curvature with surrounding inflammatory mass and adhesions. The duodenal bulb is normal and the second portion is normal except that it is dilated. I had the impression that there was partial obstruction of the second portion, perhaps by adhesions about the gastric ulcer. The patient weighs only 128 pounds and yet surprisingly the examination was rather difficult because of relaxed abdominal muscles. At times I thought I could make out an ulcer crater at the greater curvature of the antrum. At other times it seemed that this might possibly be an ulcer or diverticulum in the second portion of the duodenum.

"Impression: Frank lesion of some sort involving pyloric antrum and second portion of duodenum, probably gastric ulcer. Am trying to repeat this part of the examination."

"Second roentgen-ray examination: Findings are approximately as before. That the pyloric antrum is frankly abnormal and that the second portion of the duodenum is dilated there can be no doubt. There may possibly be a large shallow ulcer crater on the greater curvature of the pyloric antrum but the appearance is by no means typical.

"Impression: Frank lesion pyloric antrum and probably also second portion of duodenum, nature not determined."

The gastroscopic examination by Dr. Rudolf Schindler on December 9 was described as follows (see figure 2):

"There was half an ounce of stomach contents containing no acid.

"The patient was very coöperative and the whole stomach was seen. The view of the antrum revealed immediately an extensive pathology. The antrum was narrowed by a stiff infiltration and there were reddish nodules protruding from the anterior wall. The circumference of the angulus was infiltrated, also, and within this infiltration two ulcers were seen. The one ulcer toward the lesser curvature was pinkish gray in color with not definitely blending edge, surrounded by a rather flat stiff wall, which was only half a centimeter thick. The mucosa above this wall looked normal. The second ulcer lying in a diffuse infiltrated area had no wall.

FIG. 2. Gastroscopic picture of gastric syphilis, simulating carcinoma. The narrowed slit-like cavity of the antrum is seen in the center. It is surrounded by stiffly infiltrated mucosa. Extensive ulceration is present. At the left lower margin there is a wall-like elevation, rather sharply limited toward the normal mucosa coming into the field from 6 o'clock.

"It was difficult to tell how far the infiltration of the posterior wall extended upward. However, the limiting wall of the lesser curvature was located 13 cm. below the cardia and at 10 cm. below the cardia no infiltration of the posterior wall was visible. The lesser curvature and anterior wall above this area showed an almost complete atrophy, thinning, grayish to white color with many blood vessels.

"Impression: (1) Carcinoma, Type III, of the antrum limited by a wall at the lesser curvature but diffusely infiltrating the posterior wall. (2) Extensive atrophic gastritis. (3) Type III carcinoma usually does not give a good prognosis but in this case the upper margin is so far distant from the cardia that, in my opinion, the attempt of a resection must be made.

"Note: After gastroscopy I learned that the patient has a positive Wassermann. While gastric lues should be considered, notwithstanding, I still feel that this is a neoplastic lesion."

The presence of an ulcerative lesion of the gastric antrum was clearly indicated by the evidence presented. The differential diagnosis involved primarily peptic ulcer, carcinoma and syphilis. The location of the ulcer and its roentgenologic and gastroscopic manifestations did not fit with the diagnosis of benign peptic ulcer.[32] On the other hand, the picture was entirely compatible with syphilis or carcinoma. The posi-

tive history favored the former diagnosis; the greater frequency of carcinoma favored the latter. Positive differentiation could be made only by histologic study of the tissue or by continued observation under antiluetic therapy. Surgery was advised because it would give a prompt and decisive answer to the question and also because, if carcinoma were found, the patient would thus have been given the benefit of rather early surgical treatment. Consequently, operation was performed by Dr. Lester Dragstedt December 16, 1940, the tentative diagnosis being (*a*) gastric syphilis or (*b*) gastric carcinoma. The abdomen was opened through a right paramedian incision. The peritoneal cavity contained free fluid. The omentum was normal in appearance. The

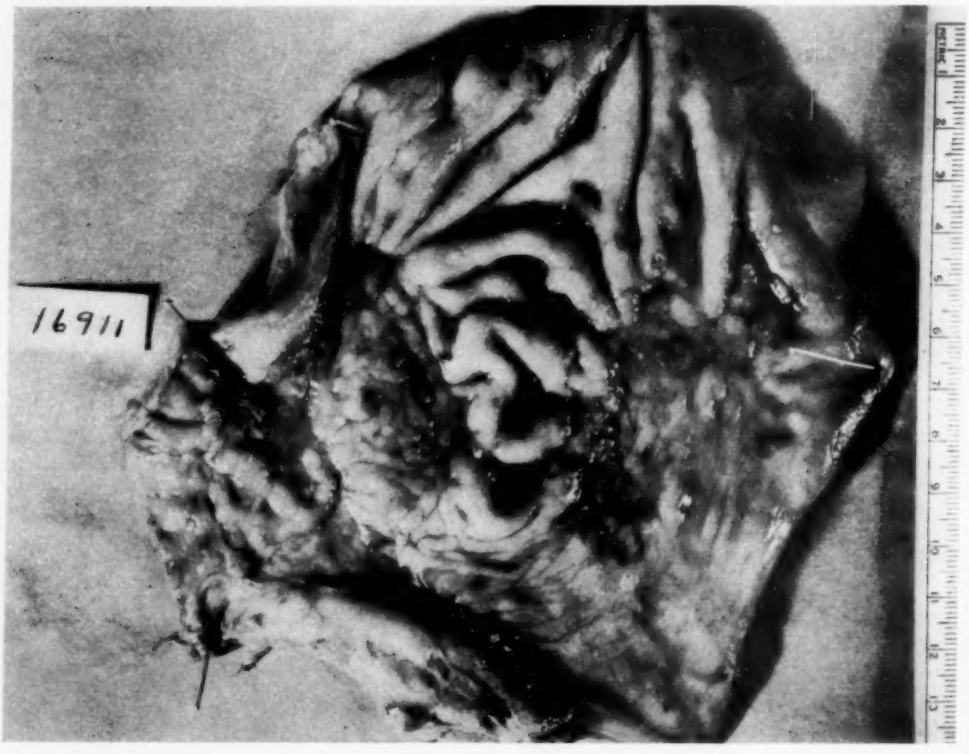


FIG. 3. Ulcerative gastric syphilis showing the serpiginous configuration of the prepyloric ulcer and, on section, the thickening of the wall. The pylorus is at the left facing the identification tag. The distal edge of the ulcer adjoins the pylorus and is partially hidden by the overlying gastric wall seen on longitudinal section.

serosa over the stomach and duodenum was normal. The cardia and fundus of the stomach were normal to palpation. The gastric antrum was thickened and had a resilient consistency. There were no areas of hardness to suggest carcinoma. Several enlarged lymph nodes were observed along the lesser curvature. A partial gastrectomy was performed.

The pathologic description of the resected specimen (figure 3) is as follows:

"The specimen consists of the lower two thirds of the stomach and the first 3 cm. of the duodenum. The entire antral region including the pylorus is thickened but soft. There are numerous hyperplastic lymph nodes in the attached mesentery. The serosal surface is smooth and shining. At the pylorus the lumen of the stomach is narrowed

to a diameter of 1.7 cm. The proximal mucosa appears slightly edematous, but otherwise normal. Beginning about 5 cm. from the proximal end of the resected specimen on the greater curvature and extending along the anterior wall to the antrum is a nodular irregularity of the mucosa from which region the folds of normal mucosa radiate outward. This nodular area measures 7 cm. in diameter and is continuous with a similar area of involvement in the pyloric and prepyloric regions. The mucosa of the entire prepyloric region, pylorus and upper duodenum is nodular. The gastric wall, however, is soft and pliable. Extending around the pylorus, except for a band of intact mucosa 3 mm. wide, is a shallow ulcer of irregular shape measuring 3.5 by 4.3 cm. in longest diameters. The base of the ulcer is smooth and dark brownish-red. The margins of the ulcer are raised only slightly and there is little apparent infiltration of the mucosa surrounding the ulcer. The base of the ulcer lies in the submucosa and there is no more gross infiltration of the base of the ulcer than there is throughout the entire wall of the antral region of the stomach. The ulcer margins are only very slightly rolled. In the prepyloric region the gastric wall is 8 mm. thick while at the proximal end it is 3 mm. thick. In the thickened region the wall has a glassy appearance similar to, but softer than, that of scirrhous carcinoma."

The important histologic features of the lesion may be seen in figures 4 to 8.

The outstanding characteristics of this gastric lesion are accumulations of inflammatory cells, both diffuse and perivascular; scattered small follicle-like groups of round cells and gummatoid or tuberculoid granulomata; and a large but quite superficial ulcer. Necrosis is evident only on the floor of the ulcer which has a base of very vascular and cellular granulation tissue, topped by a fibrinous membrane. The invading cells are mainly lymphocytes and plasma cells, with quite a few eosinophiles in some regions, and occasional neutrophiles. Epithelioid and giant cells are found only in the small granulomata which are invariably closely associated with blood vessels. No organisms (bacteria, yeasts, fungi or spirochetes) can be identified in suitably stained sections.

Perivascular round cells and inflammatory changes in the blood vessels are the lesions most suggestive of syphilis. Many large and small blood vessels, arteries as well as veins, located in all parts of the antral wall, are ringed by lymphocytes and plasma cells. Arteritis is relatively mild although many arteries show, besides the periarteritis, a focal or general proliferative intimitis. In a few small arteries the lumina are appreciably narrowed, and in some of them lymphocytes are scattered through the thickened intimas. Many veins show a similar mild phlebitis. The most conspicuous venous lesions are of two categories, one affecting large veins, deep in the gastric wall; and the other involving small veins and particularly those of the thick submucosa. Multiple and serial sections demonstrate that vascular lesions are focal or segmental and that they are most numerous in the neighborhood of the ulcer.

At first glance the lesions of the larger veins appear to be nodular granulomata, located deep in the submucosa or within the muscle coat (figures 4 and 5). These nodules are composed largely of epithelioid cells, giant cells, lymphocytes and connective tissue. The relationship to veins becomes obvious in sections stained so as to demonstrate elastic tissue (figure 6), and in segments in which a part of the venous wall is intact (figure 7). The pathologic condition is plainly a panphlebitis, with narrowing or obliteration of the lumen by granulomatous tissue. Miliary nodules, presumably small gummata, may be found in the adventitia, among the remnants of the media, or in the tissue filling the lumen. These nodules are aggregates of epithelioid cells which incorporate a few lymphocytes, and often surround a giant cell. They are looser in structure than the classical small tuberculous nodule and the giant cells are more pleomorphic than is usually the case in tuberculosis. No caseation is seen. The appearance of some segments of veins (figure 7) suggests that the inflammatory changes originate in the adventitia, perhaps by extension from the perivascular

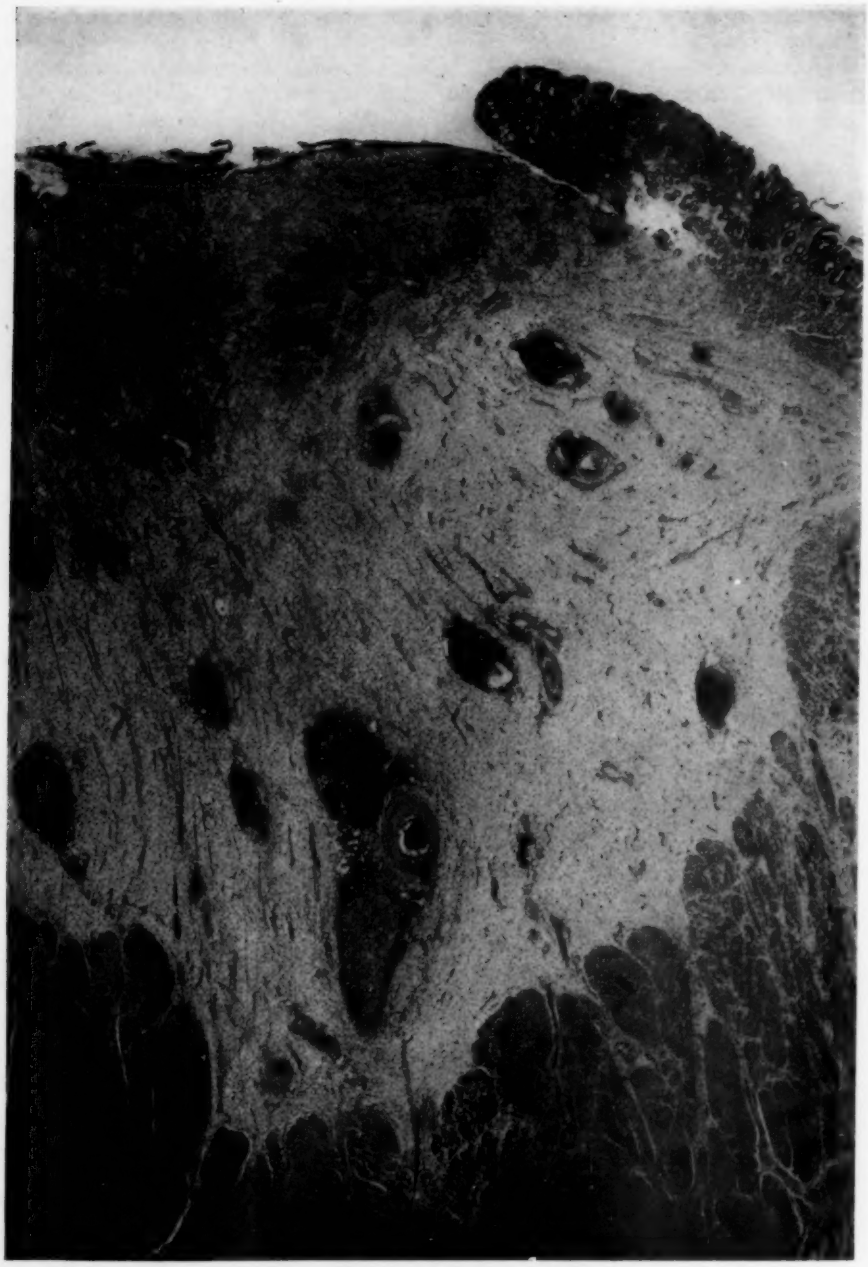


FIG. 4. Syphilitic gastric ulcer. The shallow ulcer has a base of very vascular and cellular granulation tissue and is covered by a membrane rich in fibrin. Note the thick edematous submucosa with follicular aggregates of round cells, the interstitial inflammation of the tunica muscularis, and the gummatous phlebitis affecting a large vein deep in the submucosa. See figures 5, 6 and 7 for details of the phlebitis (in sections of the same vein at different levels) and figure 8 which illustrates a follicular lesion. Hematoxylin and eosin, × 16.

FIG. 5. Panphlebitis in syphilitis of the stomach. This photomicrograph of the vein shown in figures 4, 6 and 7 demonstrates the difficulty in identifying the venous wall. The lumen is occluded, and giant cells and two miliary gummata are discernible. Hematoxylin and eosin, × 165.

FIG. 6. Panphlebitis and mild arteritis in syphilis of the stomach. Here the vein shown in figures 4, 5, and 7 can be identified by the darkly stained remnants of its elastic fibers. Two miliary gummata are visible in the granulomatous tissue which replaces the lumen. The periarteritis and mild arterial intimitis are illustrated, as is the interstitial exudate in the tunica muscularis of the vein. Weigert elastic tissue and Van Gieson stain, × 110.

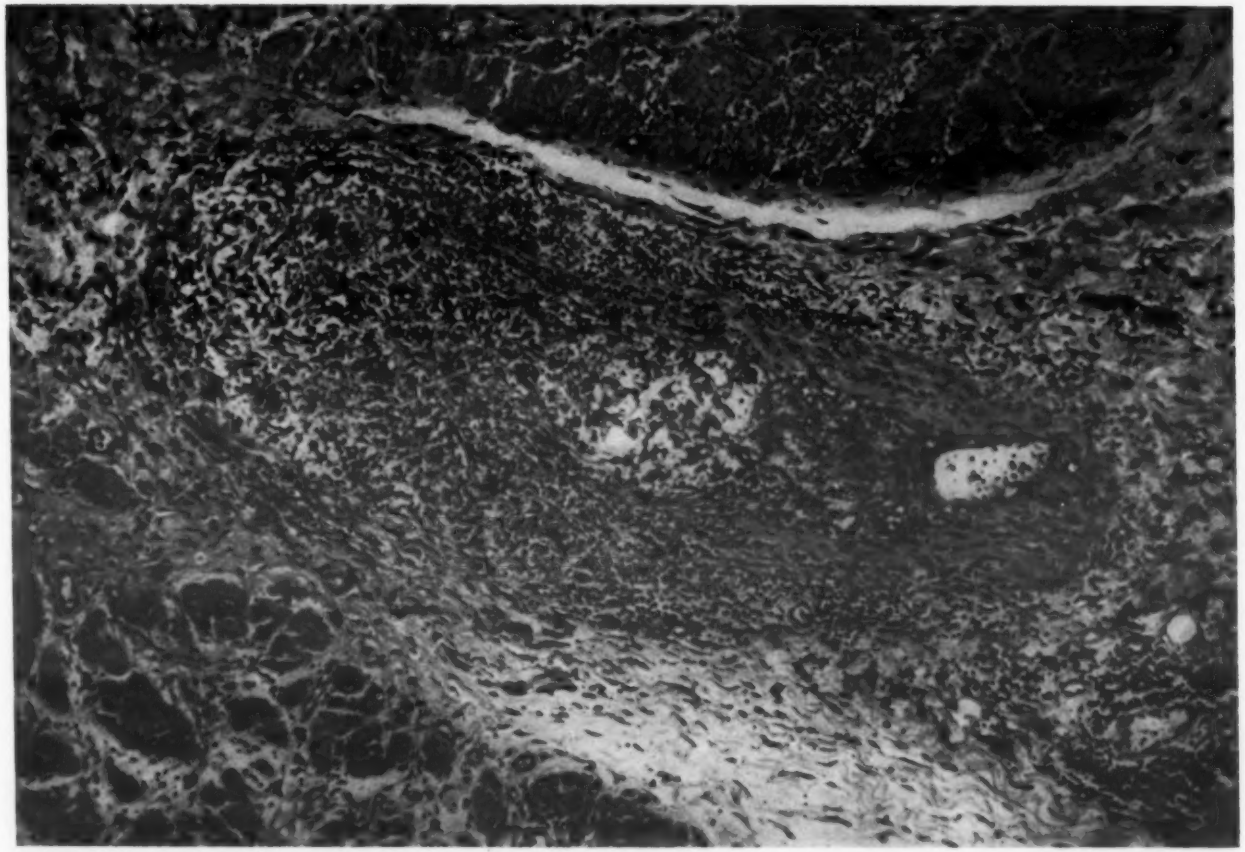


FIG. 7. Panphlebitis in syphilis of the stomach. In this obliquely cut segment of the vein shown in figures 4, 5 and 6 remnants of the media and a small lumen can be recognized, and the appearance suggests invasion of the media and the lumen from the adventitial granuloma. Carbol-thionin, × 125.

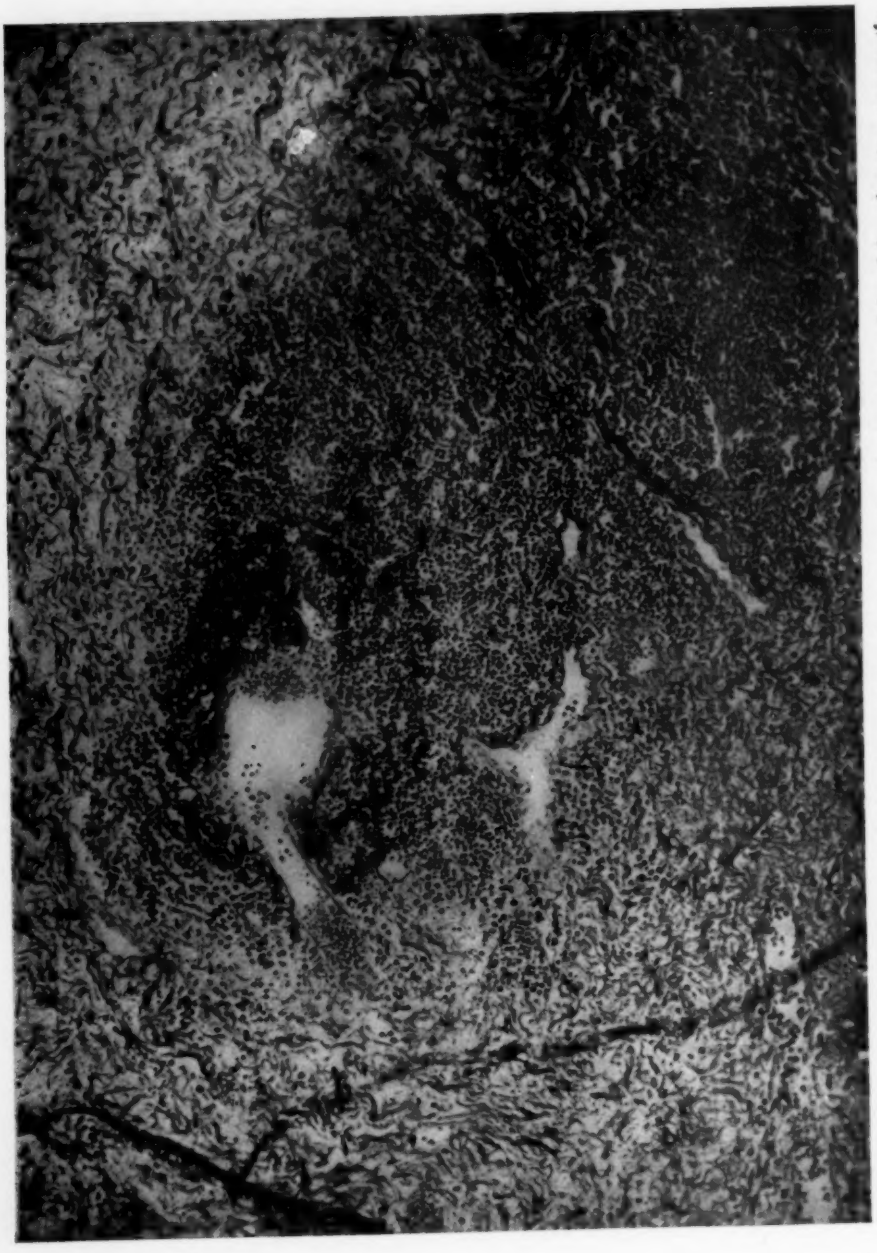


FIG. 8. Lymphoid nodule and phlebitis in syphilis of the stomach. A compact nodule of lymphocytes, apparently a lymph follicle, lies near the lower right corner. About it lymphocytes and plasma cells invade the loose stroma and penetrate the wall of a small vein. Some of the small vascular spaces are lymphatics. Weigert elastic tissue and Van Gieson stain, × 125.

lymphatics. There is no proof that thrombosis plays a part in obstructing the lumina of veins.

Some features of the lesions of the smaller veins, too, seem to point to the perivenous lymphatic channels as the primary site of exudation. The central portions of many of the follicle-like lesions so numerous in the submucosa (figure 4) actually seem to be lymph follicles. These globular aggregates of lymphocytes usually lie near or in contact with the veins. They have less compact mantles of loose connective tissue infiltrated by plasma cells and lymphocytes, and often including one or more wide lymphatic vessels. The round cells may invade the vein wall (figure 8). The lumen of the vein may be narrowed or occluded, a fact apparent in sections stained by the Weigert method, in which elastic fibers outline the obliterated channels.

Several other features deserve special comment. The ulcer is nowhere deeply excavated (figure 4), and in some regions bundles of the muscularis mucosae persist in its floor. The mucous membrane is thin in places, with widely separated and atrophic glands. In other regions the glands are simplified and some crypts are cystic. In most sections from the antrum the stroma is loose, invaded by plasma cells and eosinophiles, with occasional lymphocytic follicles. The mucosa is more normal and of the fundic type in sections from the proximal border of the resected segment. Several factors are responsible for the marked thickening of the submucosa (figure 4). These include the granulation tissue and exudate, some general increase of fibrous tissue, and marked edema. Blocking of lymphatic channels is probably a major factor in causing the edema, since wide lymphatic vessels abound in all parts of the wall. Inflammation of the muscle coat is diffuse and extensive beneath the ulcer (figures 6 and 7). It is in this interstitial exudate that eosinophiles are especially numerous. Elsewhere in the muscular layers the infiltration is perivascular, or about nervous elements, and most of the cells are of lymphoid types. Serosal involvement is similar, and is slight except in regions below the ulcer. Here there are larger foci of lymphoid cells in the very edematous peritoneum. The gastric lymph nodes show a lymphocytic hyperplasia with prominent cortical and medullary follicles, and without focal or specific lesions. However, plasma cells invade the areolar tissues about their capsules. Besides a few perivascular foci of round cells the duodenum shows only a superficial catarrhal inflammation.

Comment

From the point of view of gross and microscopic pathology, there are no absolutely pathognomonic lesions of gastric syphilis, or indeed of syphilis anywhere in the body. In most cases the diagnosis must rest on presumptive evidence. The characteristics of the gastric lesion here presented are certainly similar to those of reported cases in which there is little doubt of the syphilitic etiology.[9, 25, 13, 31] Especially noteworthy are the predilection for veins and the unusual types of venous lesions. The diagnostic importance of panphlebitis (or periendophlebitis) in gastric syphilis has recently been reëmphasized by Williams and Kimmelstiel.[31] These authors preferred the term, periendophlebitis, as it stresses the progression of the inflammatory reaction from without to the lumen. Our failure to demonstrate spirochetes is not to be considered a valid argument against syphilis. In most of the late lesions of syphilis the histologic demonstration of spirochetes is rarely unequivocal. All in all, with so many features in common with the best authenticated cases and with so little to hint of any other etiology, it seems quite proper to attribute the unusual gastric lesion of this patient to syphilis. It is almost certainly an example of ulcerated gummatous syphilis, using the term gummatous in its broadest sense as applicable to all late syphilitic lesions which terminate in scarification.

The clinical picture was perfectly compatible with gastric syphilis, but certainly not pathognomonic of such a lesion. The known presence of syphilis and the age of the patient favored the diagnosis, but neoplastic lesions occur not infrequently in individuals of this age and in known syphilitics. The roentgenologist very properly described the abnormal appearance of the outline of the barium-filled gastric antrum, the alterations in the mucosal pattern, and the presence of a crater. The differentiation of the various possible causes of such morphologic alterations is, of course, a conjecture based on the nature and the location of the changes observed and upon consideration of frequency and probability. In this instance the roentgenologist recognized the fact that the lesion was unusual, but did not feel justified in attempting to distinguish between the changes produced by carcinoma, peptic ulcer, syphilis, or other gastric lesions. The soundness of this point of view is evident, we think, from the pathologic features described. The gastroscopist, likewise, and for the same reasons, was unable to make an absolute differentiation. The question as to whether under such circumstances it is better to advise surgical therapy or a trial of antisyphilitic treatment cannot be answered dogmatically. The answer is in part a matter of opinion and in part dependent upon the various conditions present in the case under consideration.

The gastroscopic observation of this case has demonstrated that it may be impossible to differentiate gastroscopically carcinoma and syphilis. The picture seen definitely excluded a benign peptic ulcer, but was rather characteristic of a carcinoma, Type III according to the gross Borrmann classification, consisting of an ulcer within an outspoken stiff infiltration, this infiltration being partially diffuse, partially walled off. It is true that the soft pinkish color of the ulcer floor (characteristically different from the brownish-red color observed in the gross bloodless specimen) was unusual; there was, furthermore, an unusual glistening smoothness of the ulcer floor not mentioned in the protocol. However, there is such a wide range in the various colors and aspects of carcinomatous ulcers that these points seem to be of questionable diagnostic value for future cases.

The gastroscopic literature contains but few reports on gastric syphilis. One of us [21] observed, in 1923, hourglass formation and extensive gray scarring of the mucosa above the constriction in a case of neurosyphilis and thought these changes might have been the end result of a treated gastric syphilis. In another case numerous small scars were seen in the stump of a stomach, a portion of which had been resected because of proved gastric syphilis.[22] Tumefaction has been observed in untreated cases. Dr. Leon Schiff of Cincinnati saw a tumor-like protrusion of the posterior wall of the stomach with multiple small ulcerations in a syphilitic colored girl. Some time after the institution of antisyphilitic treatment, one of us (R. S.) had the privilege of looking into this stomach. A diffusely infiltrating thickening of the posterior wall, indistinguishable from a carcinoma (Type IV) was seen; the ulcer had disappeared. This patient had an uneventful recovery. An almost identical picture was observed by one of us (R. S.) in a colored girl at Cook County Hospital. The carcinoma-like infiltration disappeared entirely under antisyphilitic treatment. Even retrospectively in these two cases the differential diagnosis from carcinoma would have been impossible by the gastroscopic picture; the therapeutic test suggested, and indeed, probably confirmed the diagnosis of gastric syphilis, but no microscopic exami-

nation was possible. The recent German gastroscopic literature [6] does not contain any report on gastric syphilis, but in the French gastroscopic literature, gastric syphilis is considered to be a frequent finding. Moutier [15] distinguishes gastroscopically four different forms: (1) hemorrhagic, (2) ulcerative, (3) gastritic, and (4) tumorous. Microscopic confirmations of the diagnoses are not presented and the case histories are not always conclusive. However, a colored picture published by Moutier is quite remarkable. Within a nodular, stiff, tumor-like infiltration a large shallow ulcer is seen, the color of which is a dark yellow, quite different from the color seen in benign ulcers and most carcinomata. After treatment this ulcer disappeared. Moutier, however, believes that there is a close relation between cancer and syphilis of the stomach ("un flirt entre la syphilis et le cancer"),[15] and believes that there exist true gastric cancers of syphilitic origin which may be cured.[16] This unique conception may have influenced his gastroscopic interpretation.

The gastroscopic observation and the microscopic study of our case revealed the presence of a severe atrophic gastritis in addition to the tumor formation, a frequent finding, of course, in gastric carcinoma. The atrophic gastritis may account for the histamine-proved anacidity found in a high percentage of cases of gastric syphilis and for the very low acidity, including on one occasion achlorhydria to histamine, demonstrated in the present case.

Summary

The clinical, roentgenologic, gastroscopic and pathologic features of a gastric lesion considered to be ulcerated gummatous syphilis are described and briefly discussed.

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PAROXYSMAL AURICULAR FIBRILLATION IN ASSOCIATION WITH HIATUS HERNIA; REPORT OF A CASE*

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Paroxysmal auricular fibrillation has been described many times. The inciting factors are numerous, varied, and often difficult to determine. This arrhythmia may take place in the presence of organic heart disease as well as in hearts which show no variation from the normal. Not infrequently, the inciting factor is due to alcoholic drinking or to some gastrointestinal disorder.

The association of hiatus hernia with heart disturbances is now well established. Harrington,[1] in a review of 60 cases of hiatus hernia, had seven cases

* Received for publication June 8, 1942.

which were diagnosed as heart disease. Recently, Gilbert [2] stated that hiatus hernia may induce attacks of paroxysmal auricular fibrillation, the arrhythmia coming on with the protrusion of the stomach into the esophageal hiatus and disappearing when the stomach slips back into place. The occurrence is mediated through the vagus. An understanding of the vagus and its distribution will enable one to appreciate the association of the esophagus, stomach and heart through the nervous system.

The vagus nerve is composed of parasympathetic efferent, somatic motor (special visceral efferent) and sensory fibers. It arises in the medulla oblongata and passes through the neck and thorax to the abdomen. The right and left branches join to form the esophageal plexus. From this plexus one trunk is formed which goes through the diaphragm on the posterior wall of the esophagus and is distributed to the posterior surface of the stomach. Arising from the esophageal plexus is another branch which passes through the diaphragm on the anterior surface of the stomach.

There are two other branches of the vagus nerve—the superior and inferior cardiac. The superior cardiac arises from the vagus in the neck; the inferior cardiac arises from the vagus as it lies by the side of the trachea and also from the recurrent nerve. All the branches contain parasympathetic efferent and sensory fibers.

During the act of retching and vomiting the branches of the vagus may be stimulated with a resulting excitation of the fibers to the heart, followed by a disturbance of rhythm. Also during severe vomiting, the herniation may be exaggerated with resulting pressure on the lower portion of the esophagus and stimulation of the esophageal plexus.

The following case is being reported because of the occurrence of paroxysmal auricular fibrillation in an individual with hiatus hernia.

Case Report

D. R. J., a male, aged 44, was suddenly taken ill with a rapid irregular beating of the heart. This followed an attack of severe headache, retching and vomiting brought on by an overindulgence in alcohol and food. After considerable retching he complained of a fluttering sensation in the chest and some shortness of breath. The attack lasted for about 48 hours and a normal rhythm was established after he had taken 0.6 gram of quinidine.

The patient stated that since early childhood he had had recurrent attacks of sick headache, unilateral in nature, associated with gastrointestinal upsets and vomiting. After maturity these attacks were brought on by worry, fatigue, or indiscretions in diet or drink.

Between 1922 and 1925, while the patient was in medical school, the headaches became severe and incapacitating. It was during a severe attack that he first developed a peculiar sensation in his chest, this following an episode of vomiting. The sensation disappeared within 24 hours and after this time he felt perfectly well. During every attack of sick headache and vomiting he had thereafter, he noticed this peculiar sensation in the chest associated with an irregularity of the heart. These attacks subsided spontaneously within 24 to 36 hours. In 1932 he began to take digitalis with no appreciable effect on the arrhythmia. In 1941 the patient had a gastrointestinal series done because of a recurrence of indigestion and symptoms suggestive of a peptic ulcer. The roentgenograms showed a paraesophageal hiatus hernia (figure 1). A Graham test done at the same time showed a normally functioning gall-bladder.

The following series of electrocardiograms show the sequence of events which took place during a recent attack. The first electrocardiogram was taken during a routine physical examination of the patient 11 days before this attack and shows a normal sinus rhythm. On inspection of the second and third records it may be seen

FIG. 1.

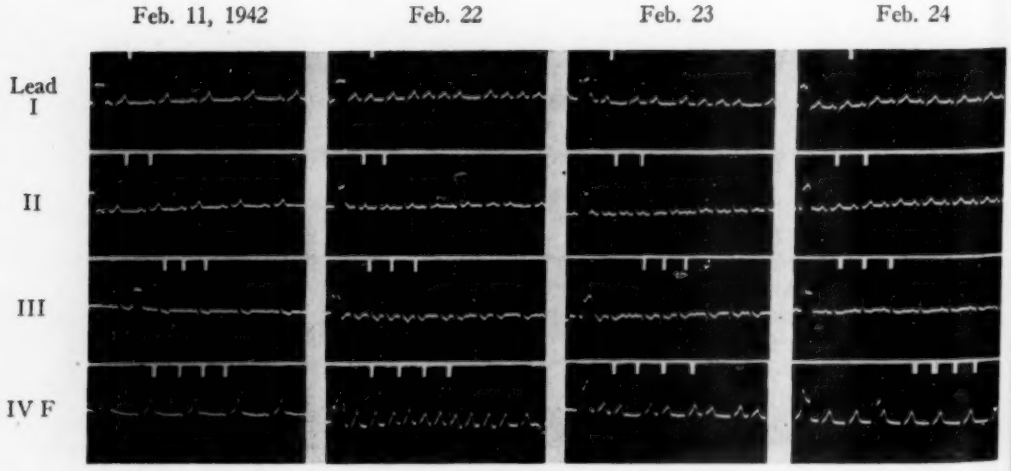

FIG. 2.

that there is auricular fibrillation with electrical alternans. In addition to the fibrillation there are periods of what appear to be nodal coupling and periods in which the ventricular groups are very regular. These may represent auricular fibrillation with regular ventricular rhythm as described by Levy [3] and others. The last electrocardiogram of the series shows a return to a normal sinus rhythm 48 hours after the onset of the arrhythmia.

Summary

1. A case of paroxysmal auricular fibrillation occurring in a patient with hiatus hernia is reported.

2. Hiatus hernia should be searched for in a person with paroxysmal tachycardia.

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EDITORIAL

VITAMIN DEFICIENCY AND LIVER DISEASE

The relation of vitamin deficiency to liver disease may be approached from two angles: (1) vitamin deficiency as an etiologic factor in the production of liver disease; (2) the rôle of preëxisting liver disease in the development of certain vitamin deficiency states.

An abundance of experimental evidence attests to the etiologic rôle of vitamin deficiency in the production of liver disease. MacLean and Best [1] in 1934 reported that fat was deposited in the livers of rats kept on a high-fat intake and that this fatty deposition could be prevented by giving adequate choline (now generally regarded as a member of the vitamin B complex). Subsequently, György and Goldblatt [2] produced fatty livers with necrosis in rats maintained on a diet deficient in the vitamin B complex even though supplemented with thiamin, riboflavin, and pyridoxin. The addition to the diet of yeast, a yeast extract, or 2 milligrams of choline a day usually prevented the changes in the liver. Rich and Hamilton [3] succeeded in reproducing true cirrhosis of the liver in rabbits fed a deficient diet. The development of cirrhosis was not prevented by the addition of thiamin, riboflavin, pyridoxin, nicotinic acid, or vitamins A, D, and E to the basal diet, whereas a supplement of 5 grams of dry brewer's yeast a day gave full protection.

Interpretation of disease in man in the light of experimental work in animals must be made with the utmost of caution. However, certain clinical observations suggest that vitamin deficiency may be an all-important etiologic factor in fatty liver and cirrhosis of the liver in human beings. Fatty liver is frequently encountered in patients suffering from tuberculous enteritis and peritonitis, in whom decreased food intake and defective absorption from the intestinal tract are prominent features. Furthermore, fatty liver and cirrhosis of the liver are common in alcoholics who are also prone to develop other deficiency diseases such as polyneuritis, pellagra, beriberi, and cheilosis. Wayburn and Guerard [4] reported multiple peripheral neuropathy in 17 per cent of a large series of cirrhotic patients. Incontrovertible evidence that ethyl alcohol per se can produce cirrhosis or any of the other recognized deficiency states just enumerated has never been established. The trouble with the severe alcoholic is that he forgets to eat, and it seems plausible to assume that these various morbid states to which

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[4] Wayburn, E., and Guerard, C. R.: Relation between peripheral neuropathy and cirrhosis of the liver, Arch. Int. Med., 1940, lxvi, 161.

an alcoholic is subject are primarily manifestations of vitamin deficiency. Conceivably alcohol may exert a toxic effect in the face of a poor diet, but the rôle of alcohol must be a minor one at best, since all of the deficiency syndromes may develop in total abstainers on deficient diets. Patek [5] has observed remarkable improvement in patients with cirrhosis who were treated with a diet high in protein, carbohydrates, and vitamins, supplemented with large doses of brewer's yeast and liver extract. Ascites cleared up permanently in a number of his patients. Snell [6] has reported similar results with a high carbohydrate, high vitamin therapeutic regimen. Thus, there appears to be a significant relationship between nutritional deficiency and cirrhosis of the liver, both from the standpoint of clinical manifestations and from the results of high vitamin therapy in cirrhotics.

Now to turn to the other side of the ledger, the rôle of preëxisting liver disease in the development of certain vitamin deficiency states. Liver disease may contribute to deficiency of the fat-soluble vitamins A and K in one of three ways: (1) failure of proper absorption in patients with jaundice; (2) failure of storage of the vitamin in the diseased liver; (3) disturbance of intermediary metabolism of the vitamin in the damaged liver. In patients with obstructive jaundice or hepatitis, the lack of bile salts in the intestinal tract results in poor absorption of fats and fat-soluble vitamins.

Vitamin A deficiency is recognizable by any one of three methods: dark adaptation test, chemical determination of vitamin A in the blood, and typical pathologic changes such as epithelial metaplasia and keratinization. Defective absorption of vitamin A and carotene has been demonstrated in children with congenital atresia of the bile ducts [7] and in patients with catarrhal jaundice. These clinical observations receive experimental support in bile fistula rats in which changes in vaginal epithelium were used as a criterion of vitamin A deficiency. Carotene furnishes the chief source of vitamin A in the average diet, and the normal liver converts carotene to vitamin A through the action of an enzyme carotenase. Testing liver slices in vitro, Olcott and McCann [8] found that a severely damaged liver fails to convert carotene to vitamin A. Low blood levels of vitamin A and a high incidence of night-blindness have repeatedly been described in patients with cirrhosis, while in Africa clinical keratomalacia and epithelial metaplasia of the organs are said to be common in association with various forms of liver disease. Therapy should consist in large doses of vitamin A administered orally along with bile salts or large parenteral injections of vitamin A. Little improvement is to be expected from a high carotene intake in patients with severe liver damage.

[5] Patek, A. J., and Post, J.: Treatment of cirrhosis of the liver by nutritious supplements rich in vitamin B complex, Jr. Clin. Invest., 1941, xx, 481, 505.

[6] Snell, A. M.: Recent advances in treatment of hepatic disease, Minnesota Med., 1940, xxiii, 551–556.

[7] Altschule, M. D.: Vitamin A deficiency in spite of adequate diet in congenital atresia of bile ducts and jaundice, Arch. Path., 1935, xx, 845.

[8] Olcott, H. S., and McCann, D. C.: Carotenase: The transformation of carotene to vitamin A in vitro, Jr. Biol. Chem., 1931, xciv, 185.

The recognition of the etiologic rôle of vitamin K deficiency in the hemorrhagic diathesis so common in patients with jaundice represents one of the most important contributions to medical knowledge within the past ten years. The hemorrhagic tendency in jaundiced patients has been conclusively shown to be due to lowered plasma prothrombin which in turn results from inadequate absorption of fat-soluble vitamin K, failure of the severely damaged liver to utilize vitamin K in the formation of prothrombin, or a combination of these two conditions. Several satisfactory methods for measuring the prothrombin content or prothrombin time of plasma are now available; the prothrombin level is regarded as an index of the status of the individual with respect to vitamin K. The failure of jaundiced patients to absorb vitamin K may be controlled in one of the following ways: oral administration of bile salts along with crude natural sources of vitamin K such as alfalfa and fish meals or with a synthetic fat-soluble derivative of vitamin K such as 2-methyl-1, 4-naphthoquinone (1–4 mg. a day); oral administration of a water-soluble vitamin K derivative such as 4-amino-2-methyl-1-naphthol which does not require the aid of bile salts for its absorption; parenteral administration of synthetic compounds, either fat-soluble or water-soluble. If the liver is so severely damaged that it cannot produce prothrombin in spite of an adequate supply of vitamin K, bleeding will not be influenced by any of the three methods of administering vitamin K which have just been described and the prognosis becomes extremely grave. Under such circumstances, we must resort to transfusion of freshly drawn blood to supply prothrombin directly. The full understanding and proper application of these principles by surgeons and internists alike will go far toward decreasing risk from hemorrhage in jaundiced patients. The routine developed by Andrus and Lord [9] for the preoperative management of a jaundiced patient with lowered prothrombin may be taken as a practical illustration: If the jaundiced patient is bleeding on admission, he is given transfusions as a means of restoring blood lost and at the same time of administering prothrombin directly. All patients with prothrombin levels below 70 per cent (Smith-Warner-Brinkhous method) receive 2 mg. of 2-methyl-1, 4-naphthoquinone intramuscularly and the response after 24 and 48 hours is noted. If the level is still below 70 per cent, the injection is repeated every three days until normal plasma prothrombin value is restored; at most two or three injections will suffice unless severe liver damage is present. Injections may be given daily without hesitation, for there is no evidence that an excess of vitamin K will increase the prothrombin level above normal and thereby promote abnormally rapid clotting of the blood.

In addition to the special functions of the liver with reference to vitamins A and K, the liver is known to serve as a storage depot for the majority of vitamins (A, B-complex, C, D, K) and probably provitamins as well.

[9] Andrus, W. D., and Lord, J. W.: Correction of prothrombin deficiency by means of 2-methyl-1, 4-naphthoquinone injected intramuscularly, Jr. Am. Med. Assoc., 1940, cxiv, 1356.

Hence, patients with severe liver disease are bound to have inadequate reserves and are, therefore, more likely to develop outspoken manifestations of vitamin deficiency under the added strain of a severe infection or curtailment of food intake. It would seem to be established beyond the shadow of a doubt that vitamin deficiency has an important rôle in the etiology of liver disease and, conversely, that preëxisting liver disease predisposes toward the development of numerous and varied manifestations of vitamin deficiency.

W. H. B.

REVIEWS

Encephalitis; A Clinical Study. By JOSEPHINE B. NEAL, A.B., M.D., Sc.D., F.A.C.P. 563 pages; 16 × 23.5 cm. Grune and Stratton, New York. 1942. Price, $6.75.

This book on encephalitis is a fine piece of medical literature. The print is clear and legible, the mechanics of book-making well thought out, and the medical contents should be read, digested, and retained by anyone interested in the realm of encephalitis in its various manifestations.

Dr. Neal, fortunately, has had the benefit of a large financial grant, made possible by William J. Matheson, who was a victim of chronic encephalitis. Coupled with her own tremendous fund of medical experience, she has not hesitated to select as contributors several others, all of whom are well known in their respective fields.

In Chapter One, she discusses encephalitis and includes the various virus types. In Chapter Three, the neurological complications are discussed; in Chapter Four, the clinical course of epidemic encephalitis. The psychiatric sequelae are discussed by Dr. Rosner, and the behavior disturbances in childhood by Dr. Lauretta Bender. Dr. Bender has also had a great deal of experience with these encephalidides and their neuropsychiatric manifestations.

Although this book is captioned "A Clinical Study of Encephalitis," there is one fine chapter, "Number Nine," writen by Dr. Lewis D. Stevenson, in which he elaborates upon the various types of encephalitis, including congenital anomalies, infections, other viruses, parasitic, purulent, and encephalopathies due to the drugs, toxins, disturbances in the hemopoietic systems and avitaminoses. The bibliography is moderately full in this chapter, but since it is not intended to be a complete description of the various ramifications or pathology of the encephalidides, it is not to be considered adequate. To anyone interested, however, there is a sufficient bibliography to give one all the necessary leads. Mention of the several degenerative forms might have included the work of American authors from 1932 on.

This book is to be most highly recommended to students, interns, and general practitioners, as well as to those who work in the field of neuropathology and neuropsychiatry.

L. F.

Fever Therapy. By WALTER M. SIMPSON, M.D., and WILLIAM BIERMAN, M.D. 486 pages; 16 × 24 cm. Paul B. Hoeber, Inc., New York. 1937. Price, $5.00.

This volume is a compilation of the reports read at the First International Conference on Fever Therapy held in 1937. As stated in the preface, only abstracts of the original papers are published in this book, due to the fact that the papers were so numerous and so long that printing of all of the papers and of the discussions would require several volumes. This is a serious fault with the book, namely, that only from one to three pages are devoted to the subject matter and this is often inadequate. All of the authors are convinced of the value of fever therapy (pyretotherapy) and in some instances make extravagant claims. Thus regarding the treatment of early syphilis, Simpson and Kendall state "Fever therapy alone or chemotherapy alone, as applied to the control groups of patients in this study, was inadequate in a high proportion of cases"; and Neymann states that a few treatments of fever plus arsphenamine and bismuth "will cure most patients with early syphilis promptly, surely and permanently. Most cases of syphilis can thus be aborted in one or two months." It is my opinion that such statements are unwarranted and far too positive and can be made only after an observation period of from 10 to 20 years.

It is to be hoped that this form of abortive treatment will prove satisfactory, but in the past few decades some such claims have been made by others, only to be found false. In general this volume is a valuable addition to the books on fever therapy as it gives résumés of papers of all the leading investigators in this field.

H. M. R.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Sexual Glands of the Male. Reprinted from Oxford Loose-Leaf Urology. By OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S. Collaborators: FRANK HINMAN, A.B., M.D., F.A.C.S., DONALD R. SMITH, A.B., M.D., and ROBERT GUTIERREZ, A.B., M.D., F.A.C.S. 619 pages; 24 × 16.5 cm. 1942. Oxford University Press, New York. Price, $10.00.

Rehabilitation of the Tuberculous. By H. A. PATTISON, M.D., F.A.C.P. 186 pages; 23.5 × 15.5 cm. 1942. The Livingston Press, Livingston, Columbia County, New York. Price, $2.50.

The Treatment of Shock. By R. W. RAVEN, F.R.C.S. (Major, R.A.M.C.). 96 pages; 17 × 11 cm. 1942. Oxford University Press, New York. Price, $1.50.

Tropical and Sub-Tropical Diseases. By C. H. BARBER, D.S.O.–M.A., D.M. (Oxon), M.R.C.S., L.R.C.P. 189 pages; 17 × 10.5 cm. 1942. Oxford University Press, New York. Price, $1.50.

Amputations and Artificial Limbs. By R. D. LANGDALE-KELHAM, M.R.C.S., L.R.C.P., and GEORGE PERKINS, M.C., F.R.C.S. 96 pages; 17 × 11 cm. 1942. Oxford University Press, New York. Price, $1.50.

Religion and Health. By SEWARD HILTNER. 292 pages; 21 × 14 cm. 1943. The Macmillan Company, New York. Price, $2.50.

Outline of Psychiatric Case Study. A Practical Handbook. Second Edition. By PAUL WILLIAM PREU, M.D. 279 pages; 19 × 13 cm. 1943. Paul B. Hoeber, Inc., New York. Price, $2.75.

Indigestion. Its Diagnosis and Management. By MARTIN E. REHFUSS, M.D., and SUTHERLAND M. PREVOST. 556 pages; 24 × 16 cm. 1943. W. B. Saunders Co., Philadelphia. Price, $7.00.

A Handbook of Allergy for Students and Practitioners. By WYNDHAM B. BLANTON, M.A., M.D., Litt.D. 190 pages; 23.5 × 15 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, $3.00.

Familial Nonreaginic Food-Allergy. By ARTHUR F. COCA, M.A. 160 pages; 22.5 × 15 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, $3.00.

Understand Your Ulcer. By BURRILL B. CROHN, M.D. 199 pages; 22 × 14 cm. 1943. Sheridan House, New York. Price, $2.50.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,217 Fellows and Associates of the College on active military duty. Herewith are reported the names of 104 additional members, bringing the grand total to 1,321.

Theodore J. Abernethy
William B. Adamson
William H. Algie
F. Peel Allison
Charles L. Anderson

Ralph G. Ball
Maurice C. Barnes
Francis L. Barthelme
Lewis B. Bates
Zacharias Bercovitz
Elton R. Blaisdell
Morris Block
William W. Bondurant, Jr.
Ernest L. Boylen
Howard G. Bruenn
George W. Burnett

George A. Cann
Louis H. Charney
Richard J. Clark
Milton H. Clifford
Stuart R. Combs

Einar R. Daniels
J. Dwight Davis
Herman F. DeFeo
Francis G. Dickey
Preston V. Dilts
Ira Dixson
Frederic G. Dorwart
Willard G. Drown
Kenneth L. Druet
Alfred W. Dubbs
Robert B. Durham

F. George Elliott
Ralph A. Elliott
Earl B. Erskine

James M. Faulkner
Henry D. Fearon
Lucian M. Ferris

Elmer S. Gais
Leon J. Galinsky
Edward A. Greco
David S. Greenspun

Karl B. Hanson
George F. Harsh
John Harvey
Lyle E. Heavner
Philip S. Hench
J. Warren Hundley, Jr.

William K. Ishmael

Carl A. Johnson
Clarence E. Johnson
Hartwell Joiner

Edward R. H. Kurz

Lee H. Leger
George L. Leslie
Eugene J. Lippschutz
Robert E. Lyons, Jr.

James M. MacMillan
John J. Maisel
Arthur A. Marlow
Gilbert H. Marquardt
John W. Martin
Edward de S. Matthews
Edward Matzger
Charles K. Maytum
Ronald J. McNamara
Harry D. Miller
John Minor
Sylvan E. Moolten
Alvin E. Murphy

J. Ernest Nadler
J. Marshall Neely

Andrew J. Parker

Harold W. Potter
Vernon E. Powell

Harold L. Rakov
Paul H. Revercomb
Lee Rice
Andrew I. Rosenberger
J. Griswold Ruth
Benjamin H. Rutledge

S. Marion Salley
Robert L. Schaefer
Curt P. Schneider
Thornton Scott
Joseph H. Shaffer
Paul L. Shallenberger
Harry W. Shuman
Walter M. Solomon

Dale C. Stahle
Charles W. Steele
Robert E. Stone
William H. Stoner
George W. Stuppy
Verne W. Swigert

Henry M. Tabachnick
Floyd C. Taggart
Jan H. Tillisch
Herman Tarnower

Aloysius Vass

Harry A. Warren
J. Harold Watkins
Walter L. Winkenwerder
Zolton T. Wirtschafter

Dr. Ben R. Heninger, F.A.C.P., formerly of New Orleans, La., was retired from active military duty, January 31, 1943, for physical disability. Dr. Heninger is now located at Pass Christian, Miss.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Harry R. Litchfield, F.A.C.P., Brooklyn, N. Y.—"Therapeutics of Infancy and Childhood," Vol. IV and Index Vol.;
Dr. Beverley R. Tucker, F.A.C.P., Richmond, Va.—"Tales of the Tuckers."

Reprints

Dr. Nathan Bloom, F.A.C.P., Richmond, Va.—4 reprints;
Dr. George B. Dorff, F.A.C.P., Brooklyn, N. Y.—4 reprints;
Dr. Norbert Enzer, F.A.C.P., Milwaukee, Wis.—1 reprint;
Manfred Kraemer, F.A.C.P., Major, (MC), U. S. Army—2 reprints;
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Nathaniel E. Reich (Associate), Brooklyn, N. Y.—5 reprints;
Dr. Maurice S. Segal (Associate), Boston, Mass.—3 reprints;
Dr. Louis H. Sigler, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Dr. Clarence M. Trippe, F.A.C.P., Asbury Park, N. J.—1 reprint;
Dr. Edward L. Tuohy, F.A.C.P., Duluth, Minn.—7 reprints;
Joseph H. Whiteley, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—1 reprint.

Dr. Ernest E. Hadley, F.A.C.P., Washington, D. C., has contributed copies of his publications, "An Experiment in Military Selection" and "Military Psychiatry," to the College Library of Publications by Members.

A. C. P. Regents and Committees Will Meet April 3-4, 1943

The regular Spring meeting of the College Committees and of the Board of Regents will be held at the College Headquarters in Philadelphia on the week-end of

April 3–4, 1943. At this meeting the customary business transacted at the Annual Sessions will receive attention. The Committee on Credentials will review the credentials of all candidates for Associateship and for Fellowship, and make recommendations for action by the Regents. Candidates must be proposed thirty days in advance of action.

Nationwide Program for Postgraduate Seminars Being Organized for Medical Officers in the Armed Forces

In accordance with action approved by the Board of Regents of the American College of Physicians, Philadelphia, December 13, 1942, and since approved by the American Medical Association and the American College of Surgeons, these three great medical societies have combined in a program of postgraduate seminars to be conducted at Naval and Army medical installations in various parts of the country. A committee of three, one from each organization, consisting of Dr. William B. Breed, Boston, for the American College of Physicians, Dr. Alfred Blalock, Baltimore, for the American College of Surgeons, and Dr. Edward L. Bortz, Philadelphia, for the Council on Scientific Assembly of the American Medical Association, has been appointed by the respective societies, with power to act in the development of a program and putting it into action. Each College has appropriated $5,000.00, and the American Medical Association, $10,000.00. Dr. Bortz will be the Chairman and Dr. Breed the Secretary-Treasurer.

This is an extension of the work the American College of Physicians already has conducted in the field of internal medicine through the past two years. The new program will be a much larger and more inclusive one, covering the whole field of medicine.

New Life Members of the College

The following Fellows have become Life Members of the College since January 1, 1943. This is an especially auspicious time for physicians in private practice to take out life memberships; income from private practice is probably at its peak, and the College plan of life membership provides a means of underwriting one's dues during his most productive years while his income is highest, thus avoiding the burden of dues later in life. All life membership fees are deposited in the permanent Endowment Fund of the College, thus contributing to the stability and perpetuity of the organization.

Dr. Ralph K. Hollinshed, Westville, N. J.
Dr. Ranald E. Mussey, Troy, N. Y.
Dr. Eliah Kaplan, New Castle, Pa.
Dr. G. B. Kramer, Youngstown, Ohio
Dr. Spencer A. Folsom, Orlando, Fla.
Dr. Robert A. C. Wollenberg, Detroit, Mich.
Dr. Edgar F. Kiser, Indianapolis, Ind.
Dr. William Corr Service, Colorado Springs, Colo.
Dr. Harry Gauss, Denver, Colo.
Dr. Harold E. Himwich, Albany, N. Y.
Dr. Willard B. Howes, Detroit, Mich.
Dr. Joseph C. Placak, Cleveland, Ohio
Dr. Harold Riche Roehm, Birmingham, Mich.
Dr. George E. Baker, Casper, Wyo.
Dr. Charles S. Bluemel, Denver, Colo.
Dr. Samuel A. Loewenberg, Philadelphia, Pa.

New England Regional Meeting Held in Boston, February 5, 1943

The second annual Regional Meeting for the New England States was held in Boston, Friday, February 5, at Hotel Statler under the general chairmanship of Dr. William B. Breed, F.A.C.P., Governor for Massachusetts, and with the coöperation of the Governors of the New England States, Dr. Charles H. Turkington, F.A.C.P., Connecticut; Comdr. Eugene H. Drake, F.A.C.P., Maine; Dr. Harry T. French, F.A.C.P., New Hampshire; Dr. Alexander M. Burgess, F.A.C.P., Rhode Island; and Dr. Ellsworth L. Amidon, F.A.C.P., Vermont.

Dr. Earle Chapman, F.A.C.P., Boston, was Chairman of the Committee on Arrangements, and Dr. Roger I. Lee, F.A.C.P., Boston, was Chairman of the Committee on Program.

The scientific program was as follows:

Morning Session—10:00 A.M.

Presiding Officer

Reginald Fitz, F.A.C.P.

Lecturer on History of Medicine and Assistant to the Dean of the Faculty of Medicine Harvard Medical School

"Immersion Foot." James C. White, Commander, (MC), U.S.N.R.

"Observations on Immunity of Mumps." John Franklin Enders, Associate Professor of Bacteriology and Immunology, Harvard Medical School.

"Personnel Selection." C. W. Heath, W. L. Woods, L. Brouha, C. C. Seltzer and A. V. Bock, from the Grant Study, Hygiene Department, Harvard University.

"Post Concussion Syndrome." Derek Ernest Denny-Brown, F.R.C.P., Professor of Neurology, Harvard Medical School.

"Gonococcal Infections." Hugh J. Morgan, F.A.C.P., Brigadier General, (MRC), U. S. A., Washington, D. C.

"Sub-Clinical Thiamin Deficiency." Joseph Wiley Ferrebee, Associate Professor of Dental Medicine, Harvard Medical School.

"The Flight Surgeon." David N. W. Grant, Brigadier General, Air Surgeon, Army Air Force, Washington, D. C.

Afternoon Session—2:00 P.M.

Presiding Officer

James Howard Means, F.A.C.P.

Jackson Professor of Clinical Medicine, Harvard Medical School

"The Relation of the Carrier to Epidemic Meningitis." John Howard Mueller, Professor of Bacteriology and Immunology, Harvard Medical School.

"Seasickness." Robert S. Schwab, Lieutenant Commander, (MC), U.S.N.R.

"The Present Status of Electro-encephalography." Frederic Andrew Gibbs, Instructor in Neurology, Harvard Medical School.

"Problems of Immunity to Bacillary Dysentery." Rene Jules Dubos, George Fabyan Professor of Comparative Pathology and Professor of Tropical Medicine, Harvard Medical School.

"Principal Disqualifying Lesions Encountered in Military Service." Julien E. Benjamin, F.A.C.P., Lieutenant Colonel, (MRC), U. S. A., Chief of Medical Service, Lovell General Hospital, Fort Devens, Mass.

"Hearts Young and Old Under the Strain of War." Paul Dudley White, F.A.C.P., Lecturer in Medicine, Harvard Medical School.

"Primary Atypical Pneumonia." Francis G. Blake, F.A.C.P., Sterling Professor of Medicine, and Dean, Yale University School of Medicine.

"Nutrition and Resistance." Frederick John Stare, Assistant Professor of Nutrition, Harvard Medical School.

"High Protein Diet; Clinical Considerations." George Widmer Thorn, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School.

A luncheon at the Tavern Club was given by Drs. Breed and Lee in honor of Major General James C. Magee, Surgeon General of the U. S. Army, and other high-ranking officers from the Army Air Force and the Navy Medical Corps.

Many acclaimed the program as the best they had ever attended anywhere. Manuscripts of the papers will be obtained as far as possible and published in the Annals of Internal Medicine.

The evening dinner meeting, at which Dr. Breed acted as toastmaster, was addressed by Dr. James E. Paullin, President of the College, Atlanta, Dr. Ernest E. Irons, President-Elect, Chicago, Brigadier General David N. W. Grant, Air Surgeon, Army Air Force, Washington, Brigadier General Hugh J. Morgan, U. S. Army, Washington, Capt. William J. C. Agnew, representing the Surgeon General of the U. S. Navy, who was unable to be present, and by Major General James C. Magee, Surgeon General of the U. S. Army. General Magee reviewed the progress and problems in the medical service of the Army and gave many interesting facts concerning his recent extended trip to the British Isles and to North Africa.

Among other special guests at the dinner meeting were Dr. George Morris Piersol, Secretary General, Philadelphia, Mr. E. R. Loveland, Executive Secretary, Philadelphia, Dr. Edward L. Bortz, Governor for Eastern Pennsylvania, Philadelphia, Dr. George H. Lathrope, Governor for New Jersey, Newark, Dr. Asa L. Lincoln, Governor for Eastern New York, New York City, Dr. Nelson G. Russell, Sr., Governor for Western New York, Buffalo, Dr. Hugh A. Farris, Governor for the Maritime Provinces, St. John, Col. William E. Shambora, Ground Surgeon, U. S. Army, Washington, Capt. Herbert L. Kelley, District Medical Officer of the First Naval District, Boston, Col. John J. Reddy, Chief of the Medical Branch, First Service Command, Boston, Dr. Arthur W. Allen, Regent of the American College of Surgeons, Boston, Dr. James Howard Means, Past President of the College, Boston, Dr. Reginald Fitz, Regent of the College, Boston, and others.

To this meeting were invited as guests medical officers of the Army, Navy, and U. S. Public Health Service, especially those stationed in the New England area. An analysis of the registration follows:

	Fellows	Associates	Guests	Total
M. C., U. S. Army	7	4	77	88
M. C., U. S. Navy	17	3	32	52
U. S. Public Health Service .	2	–	1	3
Total, Service Men	26	7	110	143
Civilian Physicians	111	19	38	168
Total	137	26	148	311

Forty per cent of the College membership in New England was in attendance. An analysis of the geographic distribution is as follows:

Connecticut	45
Maine	8
Massachusetts	170
New Hampshire	8
Rhode Island	40
Vermont	6
Other states and countries outside of New England, including the District of Columbia, Florida, Georgia, Illinois, Maryland, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Virginia, New Brunswick (Canada), Brazil, Chile, Peru and Venezuela	34

A. C. P. Regional Meeting to Be Held in New Orleans

April 16–17

A Regional Meeting for the States of Louisiana, Mississippi, Arkansas, and Eastern Texas will be held at New Orleans at the new State Charity Hospital on Friday and Saturday, April 16–17, under the direction of Dr. Edgar Hull, Governor for Louisiana, with the aid and assistance of the College Governors for the States mentioned, namely, Dr. John G. Archer, Greenville, Miss., Dr. Oliver C. Melson, Little Rock, Ark., and Dr. M. D. Levy, Houston, Tex. Dr. Grace Goldsmith, New Orleans, is Chairman of the Committee on Clinics and Dr. John H. Musser, New Orleans, is Chairman of the Committee on Scientific Essays.

Friday and Saturday mornings will be devoted to clinics. A luncheon will be held on Friday at noon and a dinner, Friday evening. At this dinner meeting ranking authorities from the Army and Navy will present timely and interesting addresses. The meeting will end Saturday noon with a clinical pathological conference, at which the clinician will be Dr. James E. Paullin, President of the College.

All medical officers in the Armed Forces, who are stationed in the participating States, are cordially invited to attend.

By the time this notice appears in the Annals of Internal Medicine the formal programs will be organized and ready for distribution. They will be sent to all members in the States concerned and to all Army and Navy installations within those States. Other members interested may obtain copies on request from the Executive Offices of the College.

Physicians expecting to remain over night in New Orleans should apply for reservations at hotels and for reservations on trains as far in advance as possible. Address applications for hotel reservations to Dr. B. J. DeLaureal, Committee on Hotels, 3439 Prytania St., New Orleans, La.

Middle Atlantic Regional Meeting of the College

On April 24, 1943, under the chairmanship of Dr. Wallace M. Yater, College Governor for the District of Columbia, and with the combined direction of Dr. Wetherbee Fort, Acting Governor for Maryland, Dr. J. Edwin Wood, Jr., Acting Governor for Virginia, Dr. Albert H. Hoge, Governor for West Virginia, Dr. Paul Whitaker, Governor for North Carolina, and Dr. Lewis B. Flinn, Governor for Delaware, a Regional Meeting for the States mentioned will be held in Washington, D. C.

Every speaker on the program is a medical officer from the Army or Navy and an authority on his subject.

The morning session will be held at the Walter Reed General Hospital and the afternoon session, at the National Naval Medical Center at Bethesda.

Complete programs may be obtained from the Executive Offices of the College, 4200 Pine St., Philadelphia, Pa.

PROGRAM

MORNING SESSION

10:00–12:30

Walter Reed General Hospital
Washington, D. C.

1. Periarteritis Nodosa: Certain Clinical and Roentgenologic Features.
   Majors A. O. Hampton and Louis A. M. Krause.
2. Clinical Diagnosis of Lumbar Intervertebral Disc Lesions.
   Lt. Col. R. Glenwood Spurling.
3. Contrast Visualization in the Diagnosis of Intrathoracic Disease.
   Major George P. Robb.
4. Clinical Report on Primary Atypical Pneumonia.
   Capt. Dale C. Stahle.
5. Histaminic Cephalalgia.
   Lt. Col. Louis E. Lieder.
6. Simplification of Treatment of Diabetes and Diabetic Coma.
   Capt. Lazarus L. Pennock.
7. Malaria in the Army.
   Lt. Col. Thomas T. Mackie.
8. The Typhus Problem.
   Col. Harry Plotz.
9. Contact Dermatitis.
   Major Zeno N. Korth.

LUNCHEON

AFTERNOON SESSION

2:30–5:00

U. S. Naval Hospital
National Naval Medical Center
Bethesda, Md.

1. An Evaluation of the Surgical Treatment of Arterial Hypertension.
   Capt. Winchell McKendree Craig.
2. Coronary Heart Disease.
   Comdr. Arthur M. Master.
3. Experiments on Underwater Concussion.
   Capt. F. C. Greaves.
4. Practical Considerations in the Use of Blood Derivatives.
   Comdr. L. R. Newhouser.
5. The Use of Sulfadiazine in the Treatment of Meningococcus Carriers.
   Lt. F. S. Cheever.
6. Medical Problems Arising from the Return of Military and Naval Personnel from the Tropics.
   (Author to be announced.)
7. The Importance of Sub-groups and the Rh Factor in Blood Transfusions.
   Lt. J. J. Engelfried.

Demonstrations:

The Electron Microscope.
Comdr. R. H. Drager.

Blood Derivatives.
Comdr. L. R. Newhouser.

Blood Grouping.
Lt. J. J. Engelfried.

The Regional Meeting will conclude with a Dinner Meeting in the evening at a down town hotel. Many distinguished guests from among Officers of the College and ranking officials of the Armed Forces will be present. Short addresses will be made by Dr. James E. Paullin, President of the College, Rear Admiral Ross T. McIntire, Surgeon General of the U. S. Navy, Major General James C. Magee, Surgeon General of the U. S. Army, and others.

Dr. Paul G. Boman, F.A.C.P., Duluth, has been named President of the Minnesota Society of Internal Medicine and Dr. Bayard T. Horton, F.A.C.P., Rochester, Vice President.

Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., was recently renamed Secretary of the Mayo Clinic staff.

Dr. Robert P. McCombs (Associate), Nashville, Tenn., is conducting a ten-week course in internal medicine for physicians in Hamilton County (Tenn.) under the auspices of the county medical society.

Dr. John H. Fitzgibbon, F.A.C.P., Portland, Ore., spoke on "Oregon Medical Service and Situation in Kaiser Shipyards" at a meeting of the Annual Secretaries' Conference of the Indiana State Medical Association in Indianapolis, January 24, 1943.

On March 11, Dr. Clarence E. de la Chapelle, F.A.C.P., New York, N. Y., spoke on "Management of Acute Cardiovascular Emergencies" at a meeting of the Columbia County Medical Society in Hudson, N. Y., and on March 25, Dr. Norman Plummer, F.A.C.P., New York, N. Y., will speak on "Newer Chemotherapeutic Methods."

The Alumni Society of the New York City Hospital has established the James R. Lisa Award. The award will be given for meritorious work in research medicine done in the laboratories of the Hospital under Dr. Lisa's direction and will be made by him at appropriate times to the worker he selects as being worthy. The prize will consist of a medallion or parchment and of an honorarium of several hundred dollars. Dr. Lisa has been a Fellow of the College since 1935.

The 6th Annual Roger S. Morris Memorial Lecture of the University of Cincinnati College of Medicine was delivered January 8, 1943, by Hugh J. Morgan, F.A.C.P., Brigadier General, (MC), U. S. Army. General Morgan spoke on "Reflections of an 'Irregular' Army Medical Officer."

Dr. Paul S. Rhoads, F.A.C.P., Evanston, Ill., discussed "Nonspecific Pneumonia: Report of 100 Cases" and Dr. Samuel J. Lang, F.A.C.P., Evanston, discussed "Adrenal Cortical Insufficiency and Its Treatment" at a meeting of the North Shore Branch of the Chicago Medical Society on February 2, 1943.

Dr. Eugene M. Landis, F.A.C.P., Head of the Department of Internal Medicine of the University of Virginia, has resigned to become George Higginson Professor of Physiology at Harvard Medical School on July 1, 1943.

Dr. Joseph I. Linde, F.A.C.P., New Haven, Conn., was recently elected President of the Connecticut Tuberculosis Association.

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., spoke on "The Care and Feeding of Executives" at a meeting of the Chicago Conference on the Health of Industrial Workers, January 13, 1943.

Dr. George M. Decherd, Jr., F.A.C.P., has been named Associate Professor and Clinical Biochemist at the John Sealy Hospital of the University of Texas Medical Branch, Galveston.

Dr. Tinsley R. Harrison, F.A.C.P., Professor of Medicine at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., delivered the Alpha Omega Alpha Lecture at the medical college on November 24, 1942. Dr. Harrison spoke on "Cardiac Dyspnea."

Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn., addressed a meeting of the Indianapolis Medical Society on "Bleeding Lesions of the Gastrointestinal Tract," November 24, 1942.

Dr. Hugh G. Jeter, F.A.C.P., Oklahoma City, Okla., recently spoke on "Paracentetic Fluid as an Aid in Diagnosis" at a meeting of the Sedgwick County Medical Society, Wichita, Kan.

The Harvard Medical School is sponsoring a course of public lectures on medical subjects. On January 3, Dr. George W. Thorn, F.A.C.P., Boston, Mass., delivered the first lecture on "The Rôle of the Endocrine Glands in Adaptation." On January 31, Dr. Maxwell Finland, F.A.C.P., Boston, spoke on "Common Colds and Their Complications" and on February 7, Alexander Marble, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army, spoke on "The Care of Soldiers in an Army Hospital."

Dr. Fay A. LeFevre, F.A.C.P., Cleveland, Ohio, spoke on "Treatment of Coronary Heart Disease" at a "Victory Day Clinic" conducted by the staff of Mount Carmel Mercy Hospital, Detroit, Mich., on January 27, 1943.

On February 4, 1943, Dr. James E. Paullin, F.A.C.P., Atlanta, Ga., President of the College, spoke on "The Contribution of the Physician in the Present Crisis" at a special mid-winter meeting of the Rhode Island Medical Society in Providence.

The meeting of the Medical Society of Milwaukee County held in Milwaukee, Wis., January 8, 1943, was devoted to an "information please" program on Therapeutics. Among those who participated were Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn.; Dr. Ovid O. Meyer, F.A.C.P., Madison; Dr. Francis D. Murphy, F.A.C.P. and Dr. Theodore L. Squier, F.A.C.P., both of Milwaukee.

Dr. Julius H. Comroe, Sr., F.A.C.P., York, Pa., has the distinction of being the first Fellow of the College who has two sons who are also Fellows of the College, Dr. Bernard I. Comroe and Dr. Julius H. Comroe, Jr., both of Philadelphia.

The 39th Annual Congress on Medical Education and Licensure was held in Chicago, Ill., February 15–16, 1943. Dr. Felix J. Underwood, F.A.C.P., Jackson, Miss., spoke on "Medical Licensure and Public Health" and George F. Lull, F.A.C.P., Colonel, (MC), U. S. Army, Ross T. McIntire, F.A.C.P., Rear Admiral, (MC), U. S. Navy, The Surgeon General, and Dr. Thomas Parran, F.A.C.P., The Surgeon General, U. S. Public Health Service, discussed "Medicine and the War."

Dr. William H. Perkins, F.A.C.P., Dean of Jefferson Medical College, Philadelphia, Pa., recently received an honorary degree of Doctor of Science at the 156th commencement exercises of Franklin and Marshall College.

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, delivered the commencement address.

Dr. Charles F. Gormly, F.A.C.P., President of the Rhode Island Medical Society and Physician-in-Chief of the Rhode Island Hospital, Providence, was honored by the Rhode Island Dental Society. On January 27, 1943, the Society presented its medal and scroll to Dr. Gormly for "distinguished service to the community and to the dental profession."

Burroughs Wellcome & Co., of Tuckahoe, N. Y., and Sharp & Dohme, of Philadelphia, Pa., both manufacturing chemists, have been presented with the Army-Navy "E" Award. These companies are engaged in the production of immense quantities of medicinal preparations for our armed forces all over the world.

At the presentation of the award to Sharp & Dohme, Comdr. Edward L. Bortz, F.A.C.P., made the presentation address on behalf of the Navy.

SPECIAL NOTICES

DUTIES OF U. S. CITIZENS DEFENSE CORPS IN GAS DEFENSE

A program for civilian protection against gas is being rapidly developed by the Medical Division of the Office of Civilian Defense. Courses have been presented for physicians selected from the faculties of medical schools to be trained as instructors in the medical aspects of chemical warfare. Arrangements are now being made for the presentation of courses by these instructors in their own medical schools.

Training for non-medical personnel is provided in Gas Specialist Courses which since early December have been presented monthly at War Department Civilian Protection Schools. These schools are located at Amherst College, Amherst, Massachusetts; Purdue University, Lafayette, Indiana; Loyola University, New Orleans; Occidental College, Los Angeles, California; Stanford University, Palo Alto, California, and the University of Washington, Seattle, Washington.

The Gas Protection Service of the U. S. Citizens Defense Corps has been organized as follows: The Medical Division of the Office of Civilian Defense has a Gas

Protection Section responsible for organization and training for gas defense. This section functions through the nine Civilian Defense Regions, which are coterminous with the Service Commands of the U. S. Army. Regional Gas Officers have been designated for several of the coastal Regions to supervise and assist the State Gas Consultants and the Senior Gas Officers of defense councils in the organization of State and local programs. The Senior Gas Officer trains Gas Reconnaissance Agents who serve in each zone of the city. These men are responsible for the identification of the agent, the collection of samples, the prevention of casualties, the delimiting of gassed areas, and for coöperation with the Emergency Medical Service, the Health Department and other agencies concerned in protection against gas.

Instructions to members of the U. S. Citizens Defense Corps on their duties in gas defense have been issued by the U. S. Office of Civilian Defense in Operations Letter No. 104 (Supplement 3 to Operations Letter No. 42), dated January 11.

The duties to be performed before, during and after gas attacks are outlined for the following individuals and groups: State Gas Consultant, Senior Gas Officer, Assistant Gas Officers, Gas Reconnaissance Agents, Laundry Officer, Commander of the Citizens Defense Corps, Incident Officer, Air Raid Wardens, Police Services, Fire Services, Emergency Medical Service, local Health Department, Public Works, Public Utilities, Transportation Services and Emergency Welfare Services.

For the Emergency Medical Service the duties are set forth as follows:

Duties before gas attack:

1. Plan with assistance of Senior Gas Officer for the establishment of gas cleansing stations for cleansing gassed patients with other injuries and for cleansing of civilian protection personnel. Each hospital of 150 beds or more should be provided with a cleansing station. Cleansing stations should be available in the ratio of one per 50,000 population and should be located at smaller hospitals or casualty stations where 150-bed hospitals are not available in this ratio.

2. Recruit, train, and assign personnel to gas cleansing stations for cleansing services.

3. Provide instruction, in coöperation with the Senior Gas Officer, for general public and civilian protection personnel in self-protection and self-cleansing (Operations Letter 46).

4. Provide for instruction of physicians in diagnosis and treatment of chemical casualties.

5. Assist hospitals in planning for handling of gas casualties.

6. Assure adequate distribution of protective clothing and gas masks and other protective equipment to members of mobile medical teams and train personnel in their use.

7. Make provision for training drivers of ambulances and sitting case cars in protection of their equipment against liquid-gas contamination; inform them of arrangements for vehicle decontamination by Emergency Public Works Service.

8. Arrange for the protection from contamination of the equipment used to transport contaminated casualties insofar as it is possible.

Duties during gas attack:

1. Upon advice of the Senior Gas Officer and under the orders of the Commander, man the gas cleansing stations.

2. Advise other services of the U. S. Citizens Defense Corps in regard to first-aid cleansing of their personnel.

3. Assign a mobile medical team to gas cleansing stations for first aid.

Duties after gas attack:

1. Evaluate the effectiveness of the cleansing procedures which have been used.
2. Provide follow-up treatment of patients.
3. Prepare inventory of protective equipment available for use in future attacks and obtain additional equipment as necessary.
4. Cleanse bodies of the dead to facilitate identification.

Important functions assigned to the health department in the local program of gas defense are as follows:

Duties before gas attack:

1. Provide for analyses for war gases in samples of food and water. These tests may be performed in a local health department if laboratory facilities are adequate. In such case it is desirable to utilize the same laboratory facilities for the analysis for war gases of air and other materials. Where laboratory facilities other than those of the local health department are more suitable for use in the analysis of war gases, arrangements should be made by the local health department for the analysis of samples of water and food.
2. Advise the Senior Gas Officer regarding the nature of instructions to the public concerning precautions to be taken in the event of water-supply contamination. Such instructions are to be promulgated by the health officer.
3. Coöperate with waterworks officials in planning for the protection and decontamination of the water supply.

Duties during gas attack:

1. Collect samples of food and water for laboratory analysis if contamination is suspected.
2. Inform the public regarding contamination of food and water supplies, including recommendations in regard to self-protection.

Duties after gas attack:

1. Decontaminate, destroy, or otherwise provide for the handling and disposal of contaminated food supplies.
2. Assist the waterworks in the treatment of contaminated water supplies.
3. Advise the Senior Gas Officer in regard to the safety of the public water and food supplies and inform the public regarding contamination of such supplies, and methods of dealing with it.
4. Obtain reports of analyses of samples of water or food and take appropriate action. Save specimens of contaminated water and food for transmission whenever necessary to a Chemical Warfare Service or other laboratory, by the Senior Gas Officer.

Gas masks are now being distributed to the personnel of the protective services. As a guide to local distribution and care of masks, the U. S. Office of Civilian Defense issued Operations Letter No. 106, January 20.

It is recommended that masks be distributed among the protective services of the U. S. Citizens Defense Corps in approximately the following proportions: Staff, 12.5 per cent; Fire Service, 10.5; Police Service, 18.5; Air Raid Warden Service, 30; Rescue Service, 1.5; Medical Service, 12.5; Public Works, 9; and Public Utilities, 5.5.

Masks should be kept at the post where the protective personnel will assemble during drills or enemy action, not carried by them during their daily activities, the Operations Letter advises. It is recommended also that about 20 per cent of the masks

allocated to each service be stored as a reserve. It is important that the reserves be decentralized as a safeguard against destruction by fire or bombing and also to permit rapid distribution in case of an emergency.

The directive points out that since valuable and critical materials are used in the manufacture of gas masks, the utmost care must be exercised in the handling, distribution and storage. No person should receive a mask until he has been trained in its use and care, including proper storage, it is advised.

Storage must be in a cool, dry place and masks should be kept from contact with sunlight, oils and corrosive liquids and vapors. After use, masks should not be worn by another individual without proper sterilization, instructions for which are given in the OCD publication "Protection Against Gas."

Repair of masks is not to be attempted locally except in case of extreme necessity, the Operations Letter states. Broken and defective masks or those with exhausted canisters should be collected by the local Property Officer and returned to OCD Supply Depots for repair and replacement.

THE RÔLE OF THE MEDICAL DEPT. IN COMBAT
BY MAJOR NATHAN H. COHEN, M.A.C.

The primary mission of the Medical Department is the conservation and maintenance of the fighting strength of the forces in the field, and the care and treatment of the sick and injured in all the military forces. The peacetime mission of the Medical service is accomplished without much difficulty due to the fact that the medical establishments are fixed and located that all requiring medical aid may receive it instantly. The accomplishment of the wartime mission of the Medical Department is an entirely different matter which presents many great difficulties.

It is an established fact that the treatment rendered a soldier the first few hours after he is wounded, may mean the difference between complete and rapid recovery or death. Consequently, one of the most vital considerations of medical tactics is the beginning of treatment to the wounded as promptly as possible. Due to the rapidity of movement of troops in modern warfare, getting medical personnel to the wounded and evacuating the wounded to medical establishments presents a vast and complicated problem. It must be borne in mind that the primary mission of the fighting forces is the defeat of the enemy. All other considerations are secondary. Therefore the combat forces are necessarily given priority in the use of roads, terrain and the transportation of men and supplies. The Medical Department is allowed the use of only those roads and that ground which will not interfere with the movement of the combat forces. The evacuation of casualties is thus carried out with extreme difficulties as it is made against the forward movement of troops and supplies.

Each military unit has its own medical detachment which accompanies it into the field of combat and sets up its medical establishment. Some of these installations, such as the battalion aid station are located as far forward as 200 yards from the front line so that casualties may receive almost instant attention. These establishments operate while subject to the same dangers and hardships as the combat units. The Red Cross symbol no longer offers any protection against enemy attack.

Each medical unit is but a part of the fighting unit to which it is attached. Unless it understands how its team is going to play it cannot take part in the game intelligently. It is therefore necessary that medical department officers in the field are not only well versed in their professional qualifications but that they also understand the tactics and technic of the branch of the service to which they are attached. They must also be skilled in the art of military map reading and in the solution of combat

problems. Unless the tactical situation is thoroughly understood, efficient medical service cannot be rendered. With such a knowledge the commander of a medical unit can estimate where the bulk of casualties will occur, how many medical installations should be established and when and where to place them to get maximum protection from enemy fire. He can then intelligently prepare the combat orders for his unit.

It is thus seen that the Medical Department officer of today must not only be a doctor, dentist, veterinarian, etc., but also a soldier well versed in the tactics and technic of the Infantry, Cavalry, Engineers, Artillery, Air Forces and all the other branches of the service. With such a background our Medical Department may be depended upon to render the finest and most efficient medical service possible.

Dallas Southern Clinical Society

The Fifteenth Annual Spring Clinical Conference of the Dallas Southern Clinical Society, which was to be held on March 22 to 25 (inc.), 1943, has been cancelled because of the war emergency.

The Hermann M. Biggs Memorial Lecture which is held annually in Hosack Hall at The New York Academy of Medicine under the auspices of the Committee on Public Health Relations will be delivered this year on Thursday, April 1, at 8:30 p.m. by

Lt. Col. Paul F. Russell,
Medical Department, Army of United States,
Chief, Tropical Disease and Malaria Control Section,
Division of Preventive Medicine,
Office of The Surgeon General.

The subject of the lecture will be "Malaria and Its Influence on World Health." This lecture is open to the general public.

OBITUARIES

DR. LEO RICEN

Dr. Leo Ricen, an Associate of the College, died in Portland, Ore., on September 8, 1942.

Dr. Ricen was born in Odessa, Russia, in 1872. He received his B.S. degree from the Imperial University of Kazan, Kazan, Russia, and in 1901 received his M.D. degree from the University of Oregon Medical School. During 1911 and 1912 Dr. Ricen undertook postgraduate work in bacteriology at the Pasteur Institute and the University of Paris, Paris, France. During the latter part of 1912 he undertook additional work in x-ray diagnosis and gastro-enterology at the University of Vienna. He returned to the University of Vienna for additional postgraduate work in 1928.

Dr. Ricen was an instructor in the Department of Medicine at the University of Oregon Medical School from 1915 to 1920. He was also a member of the attending staff at the Emanuel Hospital from 1920 to shortly before his death. He was a member of the American Medical Association and its affiliated local, the Multnomah County Medical Society. He was also a member of the Northwest Medical Association and the Association for the Study of Internal Secretions. He has been an Associate of the American College of Physicians since 1924.

Dr. Ricen was a man of broad culture and deep intellectual attainments. The field of medicine was just one of the many subjects in which he was learned. His library of Russian literature was one of the best on the Coast. He was at home in the classics, in poetry and especially in world history. He was also a painter of considerable talent and he left some creditable art works to members of his family and friends. He was a lover of music and philosophy. Although a modest man in company, he was a brilliant conversationalist. Those who knew him valued his friendship and mourned greatly when he passed away.

HOMER P. RUSH, M.D., F.A.C.P.,
Governor for Oregon

DR. GEORGE MEADE SETTLE

On September 15, 1942, Dr. George Meade Settle, F.A.C.P., Baltimore, Md., died at the age of 62 years, after a six weeks' illness, following a coronary thrombosis. In his passing, the College has lost a staunch supporter and one who was untiring in his efforts and interests to increase the College activities in Baltimore.

Dr. George Meade Settle was born in Leeds, Md., September 9, 1880. He attended Friends School in Wilmington, Del., and received his A.B. degree in 1902 and his M.D. degree in 1905 at the University of Pennsylvania School of Medicine. He was Assistant in Neurology, 1909–1911; Instructor in Neurology, 1912–1914; Associate in Neurology, 1914–1916; Instructor in Physical Diagnosis, 1912–1914; and Associate Professor of

Neurology and Clinical Medicine, 1916 to date, at the University of Maryland School of Medicine. For many years he was Visiting Neurologist, Maryland General and University Hospitals and Hospital for Women; Consulting Physician, Harford Memorial Hospital, Havre de Grace, Md. He was a member of the Baltimore City Medical Society, Medical and Chirurgical Faculty of Maryland, and the American Medical Association; and was a Fellow of the American College of Physicians since 1927, and a Life Member of the College since 1937.

To know Dr. Settle was to love him. To have been a friend of his was something to be cherished. Those of us here who knew him so well know that in his passing he had no regrets, but his patients and many friends feel his death very keenly.

WETHERBEE FORT, M.D., F.A.C.P.,
Acting Governor for Maryland

DR. ELMER BURKITT FREEMAN

On December 23, 1942, the Maryland Chapter of the College sustained another loss in the death of Dr. Elmer Burkitt Freeman, Baltimore, who had been a Fellow of the College since 1929.

Dr. Elmer Burkitt Freeman was born at Mattoon, Ill., February 5, 1875, and died at Baltimore, December 23, 1942. He received his B.S. degree from Austin College in 1896 and his M.D. degree from the Baltimore Medical College in 1900. He was Instructor in Clinical Medicine, Baltimore Medical College, 1901–1904; Associate Professor of Clinical Medicine, Baltimore Medical College, 1904–1910; Associate Professor of Clinical Medicine, University of Maryland School of Medicine, 1913–1914; Professor of Therapeutics, Baltimore Medical College, 1910–1914; Assistant in Clinical Medicine, Johns Hopkins University School of Medicine, 1916–1922; Instructor in Clinical Medicine, Johns Hopkins University School of Medicine, 1922–1929; Associate in Clinical Medicine, Johns Hopkins University School of Medicine, 1929 to date. For many years Dr. Freeman was Physician-in-Chief, Maryland General Hospital; Assistant Visiting Physician and Dispensary Physician, Gastro-intestinal Department, Johns Hopkins Hospital; Visiting Physician, Church Home and Infirmary; Gastro-enterologist, St. Agnes Hospital; Attending Gastro-enterologist, Bon Secours Hospital, and a member of the active staff, Union Memorial Hospital. He was a Diplomate of the American Board of Internal Medicine and the author of many published papers. Dr. Freeman was a member of the American Gastro-enterological Association, the American Radiological Association, the Southern Medical Association, the Medical and Chirurgical Faculty of Maryland, and the Baltimore City Medical Society. He was a Fellow of the American Medical Association and a Fellow of the American College of Physicians. Dr. Freeman served during the first World War on the local Advisory Medical Board and was serving on Local Induction Board No. 6 at the time of his death.

The untimely death of Dr. Freeman was a severe shock to his many friends and patients. Dr. Freeman was a loyal supporter of the College and of the Maryland Chapter and never failed to do his part in making any of our functions a great success. His passing is a great loss to the teaching institutions of the city, as well as to his friends and medical associates.

WETHERBEE FORT, M.D., F.A.C.P.,
Acting Governor for Maryland

DR. HARRY BOND WILMER

Dr. Harry Bond Wilmer, noted allergist, died very suddenly at his home on January 16, 1943. Dr. Wilmer was an outstanding physician in Philadelphia and his work in the special field of allergy had gained for him a renowned position in American medicine.

He was born May 12, 1884, in Baltimore, Maryland, and attended St. John's College and the United States Naval Academy at Annapolis. He received his medical degree from the University of Pennsylvania School of Medicine in 1906. During the last World War he served as a Captain in the United States Army at Base Hospital No. 10.

For many years Dr. Wilmer was Director of the Allergy Department at Abington Memorial Hospital, and was also associated with the Allergy Department at the Graduate Hospital in Philadelphia. In addition to his other duties at Abington he held the position of Medical Director for several years.

Dr. Wilmer was a teacher as well as a practitioner of medicine. He was an Associate Professor at the University of Pennsylvania Graduate School of Medicine.

Medical activities included his membership in the American Allergic Association, having been former President of that group and the American Clinical and Climatological Society. He was a Fellow of The American College of Physicians, and in the past, has served on various committees. He was also a Diplomate of the American Board of Internal Medicine.

Sports commanded his enthusiasm in the form of yachting at which he was an expert. He was former Commodore of the Corinthian Yacht Club and the Chester River Yacht and County Club.

Dr. Harry Wilmer was loved, admired and deeply respected by his many friends and associates in and about Philadelphia. He particularly endeared himself to the membership of the College from this area by becoming intimately identified with the entertainment work associated with many regional meetings that were held here. His brilliant mind, keen sense of humor and wonderful personality have indelibly imprinted themselves in the minds and hearts of his many friends, and he will forever be remembered by them. It is indeed with humble thought and deep sorrow that we write of the passing of Dr. Harry B. Wilmer.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

REPORT AND ABSTRACT, MINUTES OF THE BOARD OF REGENTS

DECEMBER 13, 1942

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at Philadelphia, December 13, 1942, with President James E. Paullin presiding, with Mr. E. R. Loveland acting as Secretary, and with sixteen members of the Board and the Chairman of the Advisory Committee on Postgraduate Courses, Dr. E. L. Bortz, in attendance.

After reading of the Minutes of the preceding meeting and the presentation of various communications, Dr. Charles F. Tenney, who acted as a representative of the College at a meeting of the American Physiotherapy Association in New York during August, 1942, made a comprehensive report. He reported that Dr. Philip D. Wilson is Chairman of a permanent Council formed by the American Physiotherapy Association to aid in the rehabilitation of war casualties. The Council consists of seven members. It has under consideration the presentation of a bill before Congress which may have the President's support. The Council may request the organizations which were represented at the August meeting, such as the American College of Physicians, the American College of Surgeons, et al., to make a small donation to cover secretarial and other expenses. It is provided in the bill that the American Physiotherapy Association stands ready to give its services, under the direction of qualified physicians, to help rehabilitate the casualties of the present war, as well as veterans of the past war, and, in addition, other casualties such as may properly come under Government supervision.

President Paullin, for matter of record in the Minutes, reported a meeting of several Officers and Regents of the College at Philadelphia, with the subsequent approval of the Board of Regents, providing for the cancellation of the 1943 Annual Session and of future Annual Sessions for the duration of the war. A resolution was adopted approving the action of the Committee and of the mail vote taken among the Regents.

The Secretary, Mr. Loveland, presented for clarification by the Regents the following provision adopted by the Board at its preceding meeting: "The initiation fee of members serving with the armed forces and completely detached from private practice, at time of election, shall be reduced to $10.00, this regulation becoming effective as of January 1, 1942." After discussion, by resolution formally adopted, the regulation was altered to read: ". . . at time of election, *or within two months therefrom. . . .*"

The Secretary General, Dr. George Morris Piersol, reported the deaths of thirty-one Fellows and seven Associates since the preceding meeting of the Board, and the names were spread upon the Minutes. Dr. Piersol also reported four additional life members since the last meeting of the Board, making a total of 187, of whom 21 are deceased, leaving 166.

President Paullin filed a final report on the evaluation of physicians, which the College undertook in order to assist the Surgeons General of the Army and Navy in placing physicians who volunteered for military service in that type of work for which they would be best suited. This work was made possible through the very enthusiastic and hearty coöperation of a large group of physicians, Governors, Regents and members of the American College of Physicians, and other individuals. Altogether there were 369 helping in this work. Dr. Paullin's office completely evaluated and furnished information concerning 11,383 internists and 5050 pediatricians. In addition, the National Research Council requested that the general practitioners be evaluated, of whom there were about 60,000. Of these 38,000 were investigated, but the

work was discontinued because of the difficulty in obtaining adequate information. For the most part, these general practitioners were little known, were located in smaller communities, and it was found extremely difficult to appraise their qualifications. Dr. Paullin's office further evaluated 1,750 members of the Medical Reserve Corps so that, all told, this Committee collected definite information of a trustworthy nature concerning 56,184 doctors, and this information has been placed at the disposal of the Surgeons General of the Army and Navy.

Dr. Paullin further pointed out that all members of the College, Fellows and Associates, were evaluated. Data were recorded on cards, and the most complete professional detail on at least four thousand physicians was assembled that has been possible in any other organization in the United States. This information has been used in the offices of the Surgeons General, and, as a result, members of the College in particular have been assigned, in the majority of cases, to work which they can best do.

By resolution, regularly adopted, the Regents expressed their appreciation to Dr. Paullin for the enormous amount of valuable work accomplished, and, since the work is completed, discharged his Committee.

President Paullin recommended that the College should have a committee that will be able to function in an advisory capacity with some agency of the Surgeons General's offices of the Army, Navy and Public Health Service and the Office of Procurement and Assignment. He felt it necessary for the College not only to plan for the medical future but to have a committee that will be looking to post-war planning not only as it concerns members of the College but the profession as a whole.

Dr. George Morris Piersol, Chairman of the Committee on Credentials, distributed to the Board a mimeographed outline of all candidates that had been reviewed by that Committee on the preceding day. Of 193 candidates for Fellowship, 147 were recommended for election, 11 were recommended for election first to Associateship, 25 were deferred for further credentials, and 10 were rejected. Of 181 candidates for Associateship, 140 were recommended for election, 21 were deferred for further credentials and investigation, and 20 were rejected. (The list of candidates elected to Fellowship and to Associateship was published in the January, 1943, issue of this journal.)

On recommendation of the Credentials Committee, a resolution was adopted reinstating Major Rudolph A. Kocher, MRC, U. S. A., to Associateship. The application of a candidate for reinstatement as a Fellow was not approved because of lack of support by other Fellows in his community.

In accordance with provisions of the By-laws, 6 Associates were dropped from the roster because their five-year maximum term had expired without their presenting the necessary credentials for Fellowship.

The Executive Secretary, Mr. Loveland, made the following report:

"During the past year we published a Supplement to the 1941 Directory. The present membership, exclusive of today's election, consists of:

4	Masters
3,697	Fellows
1,109	Associates
4,810	Total

There are, at this date, 1,122 members serving in the Armed Forces. The average age of all members, Fellows and Associates combined, of the College is 49 years.

"We have refunded in dues to members serving in the Armed Forces over $7,000.00, and we have given credit additionally of $1,100.00. I predict that in 1943 the waiver of dues will cost us about $15,000.00, and the reduction in Initiation Fees $8,000.00.

"We have not had a resignation since the last meeting of the Board of Regents. This, out of a membership of over 4,800, I consider a record.

"We have had an increase of over 300 in the circulation of the 'ANNALS' during the past year, but we may anticipate a considerable shrinkage in the coming year, because the 'ANNALS' will not be furnished free to dues-waived members. We are attempting to offset this shrinkage by promoting subscriptions among non-members. The 'ANNALS,' however, has been placed on the approved and official lists of the Offices of the Surgeons General, and, as a result thereof, we have received numerous new subscriptions for Navy and Army hospitals.

"I wish to report further that my office is concentrating on an effort to build up income from additional advertising in the journal. With the cancellation of our Annual Sessions, manufacturers and publishers can no longer exhibit before the College; we are emphasizing the importance of their maintaining their contacts with our membership through increasing their advertising in our journal.

"I report also to the Regents that Dr. Samuel M. Poindexter, of Boise, has been appointed by the Executive Committee as the Acting Governor for the State of Idaho, serving in the place of Dr. Charles Henry Sprague.

"Dr. Thomas M. McMillan, of Philadelphia, has been elected Acting Governor for Eastern Pennsylvania, but he has not taken office due to the fact that Commander Edward L. Bortz is still located in Philadelphia and continues to serve.

"Dr. Patrick L. Ledwidge, of Detroit, has been elected Acting Governor for Michigan in the place of Dr. Douglas Donald, who is in the Service.

"Dr. Edward H. Rynearson, of Rochester, Minn., has been elected Acting Governor for Minnesota, in the place of Dr. Edgar V. Allen, who is in the Service.

"Dr. J. Edwin Wood, Jr., of University, Va., has been elected Acting Governor for Virginia, in the place of Dr. Walter B. Martin, who is in the Service.

"Dr. Charles F. Tenney, New York City, has been appointed, under provisions of the By-Laws, as a Regent of the College, to serve until the next regular election, because of a vacancy occurring through oversight of the Nominating Committee at the St. Paul Session when Dr. Irons' place on the Board became vacated due to his elevation to the post of President-Elect."

Dr. David P. Barr reported for the Committee on Public Relations. In accordance with recommendations of the Committee, resolutions were adopted providing for the waiver of the dues of five Fellows, due to illness, until their recovery and resumption of practice.

Dr. Barr reported also that two medical societies had invited the American College of Physicians to organize joint meetings with them during 1943. These invitations had been considered by the Committee and since it was thought that they may be only two of several which may be received in the future, the Committee offered the following recommendation in the form of a resolution: "It is the opinion of the Committee on Public Relations that Regional Meetings of the College are the responsibility of the College and its Governors and that the programs, together with such other activities as postgraduate seminars, examinations, etc., should be supervised by local representatives and under the direct control of the Program Committee of the College. Such Regional Meetings are, of course, open to all members of the medical profession in good standing in such communities." A motion for the approval of this resolution was made, seconded and carried.

On behalf of the Committee on Public Relations, Dr. Barr presented several additional communications, including one from Captain David W. Exley, expressing the feeling that Fellows of the College should be utilizing more than they are permitted, their special training as internists in the Army. President Paullin reported that

measures have been undertaken along this line and that no further action is required at this time. Perhaps fifteen complaints of this character have come through the College and these have been cleared through the Office of the Surgeon General. That office has always shown a ready willingness to rectify any mistakes. It was revealed that out of the 1,122 College members on active duty, reports of 15 or 20 maladjustments had been received, which is a small percentage and should be looked upon with considerable credit to the Office of the Surgeon General.

By resolution, the report of the Committee on Public Relations as a whole was adopted and the Secretary instructed to communicate with the two societies from whom invitations had been received for joint meetings.

Dr. Edward L. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, made the following report:

"This year the Committee arranged for three Courses, and you have in your hands the galley proof of the details of the curricula. Dr. Robert Cooke was unable this year to repeat his course in Allergy. Another course in general medical science planned in Philadelphia had to be abandoned because suitable arrangements could not be completed.

"The three Courses scheduled are all in Internal Medicine—No. 1 at the University of Minnesota, under Dr. Cecil Watson, and with the coöperation of Dr. William A. O'Brien, Director of Postgraduate Education; No. 2 at the Mayo Clinic under Dr. E. H Rynearson; No. 3 at Boston University under Dr. Chester Keefer. There has been a modest and wise condensation of the work of our Committee, in the face of the present altered conditions. With 25% of our membership in the Armed Forces today, it is impossible to estimate the registration. The Committee is hopeful that there will be a generous response. There has been a suggestion that the Surgeons General may assign men from their respective Services to take these courses. No fee will be required from any registrant from the Army or Navy. Men who are not members of the College, but are of College material and aspire to membership, will presumably, with your permission, be permitted to enroll in these courses upon payment of the usual fee.

"Another series of three sessions of 'Postgraduate Nights' was held in Philadelphia at the Naval Hospital this autumn. The program was an excellent one, arranged by Dr. Thomas M. McMillan, and was widely publicized in this area, not only at the Naval Hospital, but at the Army Hospital at Camp Dix. The auditorium was practically filled each evening, and the men were most enthusiastic about the program. Terminating the 'Postgraduate Nights' program, the annual Eastern Pennsylvania Round-Up was held in Philadelphia, culminating in a very spirited and enjoyable dinner meeting at the Union League, at which the College was privileged to have as its chief dinner speaker Admiral Ross T. McIntire, Surgeon General of the Navy. The whole program was so well received by officials of the Army and Navy that a request has already been made for another series of 'Postgraduate Nights' in the spring.

"Governor LeRoy H. Sloan, of Northern Illinois, likewise organized a series of 'Postgraduate Nights' at Camp Grant and at the Great Lakes Naval Hospital, culminating in a Regional Meeting for Illinois, Indiana, Iowa, Michigan and Wisconsin at Chicago on November 21. Approximately two hundred medical officers were in attendance at each program of 'Postgraduate Nights,' with a large attendance at the Regional Meeting. Outstanding representatives from the Offices of the Surgeons General appeared on the program, including General C. C. Hillman, of the Army; General David N. W. Grant, Army Air Surgeon; and Captain Robert E. Duncan, of the Navy. It would have been a good opportunity at the evening dinner meeting for an official representative of the College to have explained in some detail the activities and objectives of the College. However,

the meeting was highly successful, as evidenced by additional requests for further 'Postgraduate Nights' programs at Camp Grant and at the Great Lakes Naval Hospital. A further extension of this program is at present being developed by Governor William B. Breed for the New England States. Additional requests are coming in from other hospitals and camps throughout the entire nation. We have not extended ourselves too widely. We have proceeded cautiously, offering the facilities and the splendid teaching personnel included within the membership of this College. I have received no adverse comment. On the other hand, there has been a steady and increasing pressure for more and more activity of this kind. Here is a magnificent opportunity for the College once more to demonstrate its leadership in the field of medical education, as far as Internal Medicine is concerned. There is also a demand for instruction in other fields, especially surgery. We have been thinking about a broader program—by establishing an organization by which surgery and other specialties would be brought into the setup. In consultation with your President, the following resolution has been prepared:

"WHEREAS there has been a definite need for the extension of postgraduate facilities to medical officers of the Armed Forces, as shown by the enthusiastic attendance and response on the part of all who have attended the 'Postgraduate Nights' and Regional Meetings which have been held by the American College of Physicians during the past year and increasing urgent demands for this type of teaching, and

"WHEREAS this need for advanced training is bound to become greater the longer the war lasts, and

"WHEREAS the American College of Physicians has personnel and facilities for the development of extension courses in the form of lectures, conferences, teaching ward rounds, seminars, 'Postgraduate Nights' and round table discussions, therefore

"BE IT RESOLVED that the American College of Physicians extend its activities in this field and join with the American Medical Association, through its Council on Scientific Assembly, and with the American College of Surgeons to make a study and draw up a complete plan, listing the available personnel and, where possible, the locations for instruction, subjects to be discussed and other pertinent matters, to the end that a continuous plan of advance instruction for all doctors in the Armed Forces be furnished.

"IT IS RECOMMENDED that the Finance Committee be requested by the Board of Regents to make available funds up to the sum of $5,000.00, to be expended under the supervision of the Committee on Postgraduate Courses of the American College of Physicians toward the furtherance of this program.

"IT IS FURTHER RECOMMENDED that there be appointed a Committee with power to act, consisting of equal representation from the American College of Physicians, the American Medical Association and the American College of Surgeons to develop a program and put it into execution."

President Paullin remarked that such a comprehensive, well worked out program might be given some financial support from the Kellogg Foundation and perhaps from the Rockefeller Foundation in order to make available this type of instruction.

Dr. Henry R. Carstens, remarking upon this action, said, "I think this is a splendid idea. I attended the Regional Meeting in Chicago, and consider it one of the most delightful meetings I ever attended. Enthusiasm was great among the military attendants. There was a large delegation from Camp McCoy. The program went through with perfect precision. There was a galaxy of stars among the speakers, and every one was commenting on what a wonderful meeting it was. I hope this will be extended."

By motion, the above resolution was accepted and adopted.

By resolution, regularly adopted, Dr. Bortz' report as a whole was approved and his recommended resolution adopted.

Dr. Ernest E. Irons, Chairman of the Committee on Educational Policy, reported that Dr. Bortz' report had been formulated at a joint meeting of the Committee on Educational Policy and the Advisory Committee on Postgraduate Courses. He added, in part: "I should like to comment that our inability to hold an Annual Session may be the best thing that has happened to the College, because it gives an opportunity for developing local Regional Meetings. The local interest of men in the College is being greatly facilitated. I believe the College work is being furthered more than it would be if we had only the Annual Session."

Dr. Francis G. Blake made the following report for the Committee on Fellowships and Awards:

> "Since our St. Paul meeting, Dr. Joseph L. Lilienthal, Jr., who was awarded a fellowship to work at Vanderbilt, resigned on July first to enter the military service, and his resignation was accepted. The other two Research Fellows—Dr. James Hopper and Dr. Carl G. Heller—are now actively engaged in work, and as far as we know at present they expect to complete their fellowships this year.
>
> "When it became clear that no Annual Session would be held this year, the membership of our Committee was canvassed by mail with respect to two matters: (1) whether any fellowships should be awarded for the coming year; (2) whether the John Phillips Memorial Award should be made this year. The Committee has voted unanimously that the College discontinue awarding Research Fellowships until after the War, and that since the annual meeting is cancelled, the John Phillips Memorial Award be withheld until such time that a meeting of the College will be held."

By individual motions, seconded and regularly carried, both recommendations of the Committee were adopted.

Dr. Ernest E. Irons, Chairman, reporting for the American Board of Internal Medicine, said that the number of applications for examination, contrary to their expectations, has increased. In October, 1942, there were 307 examinees from 24 cities. In addition, there were 87 examinees in the Armed Services who took the examination in 38 different military camps. The Board has approved such methods of giving written examinations and has received the most complete coöperation from the commanding officers in various camps with but one or two exceptions. The Board during the past year had certified 193 by examination, and 20 without examination. At the time of this meeting a total of 1,038 physicians had been certified by examination and approximately 1,800, from previous actions, without examination, making approximately 2,838 thus far certified by that Board.

Dr. Irons, on behalf of the Board, asked the advice and assistance of the Regents of the College with regard to problems arising from the termination of maximum terms of some members of the Board by July 1, 1943. Dr. Jonathan Meakins, now Deputy Director of the Canadian Medical Service, is forced to resign under the strenuous conditions of his work, and the Board has accepted that resignation regretfully. "Dr. Meakins has been a power for idealism and practical application, and the Board has gone on record in the recommendation of the recognition of his very able services." The terms of two other members will expire in June. The Board is reluctant to make changes in the present war times and is looking for a method of retaining the services of these two men for the duration of the war or until they can be replaced by suitable successors.

The Board considers it desirable to introduce into membership men of the age of 45 to 55; the situation has been canvassed, but such men are not available at present

for they all appear to be in the Armed Forces; hence the Board wants to retain Dr. Reginald Fitz and Dr. G. G. Richards if possible. It was pointed out that Dr. Fitz is an appointee of the American Medical Association and that Dr. Richards and Dr. Meakins are appointees of the College.

Continuing his report, Dr. Irons said that if there are no objections on the part of the Board of Regents, the American Board of Internal Medicine will proceed with its previous decision to reduce the examination fee from $40.00 to $30.00 as of January 1, 1943. There were two reasons why the Board had suggested a reduction: (1) to coöperate in spirit with the College, and (2) it did not wish to materially increase its funds.

The final matter presented by Dr. Irons referred to certain criticisms that had been raised in a meeting of the Board of Governors of the College at St. Paul. Among these had been a communication from the Buffalo district, giving the names of candidates involved in the general complaint. The Board had drawn up a complete report on the history of each case and a communication had been forwarded through the Executive Secretary of the College, as follows: "As has been indicated repeatedly, the Board desires at all times to be fair. It is customary in conducting examinations to have a Board member and a guest examiner form an examining team, so that at least two men, and if reëxamination is necessary, four men (two of them members of the Board and two guest examiners) render opinions on the qualifications of the candidate. In a few instances the reëxamination may be conducted by a Board member only, but this is not the rule. It is of interest to note that frequently the judgment of the guest examiners, chosen for their outstanding ability and standing in the city in which the examination is held, is more severe than that of the members of the Board. It should be unnecessary to say that the intent and, I believe, always the practice of members of the Board, is to be uniformly courteous. Candidates are frequently nervous and distraught and often require encouragement before the examination can proceed. Such candidates may well misinterpret what is said to them.

"One point is to be reiterated in regard to the written examination: The examination questions frequently include questions which have perhaps no immediate clinical application, and sometimes might be regarded as catch questions. A candidate is never failed by reason of failure to answer such question. Judgment is based on his handling of the question and his ability to reason out an answer. In general, it is planned to give an examination distinctly more difficult than that which would be given to fourth-year medical students.

"In spite of all efforts to make examinations of the Board searching and still fair, it is quite possible that errors may creep in. These the Board regrets. However, the candidate may repeat the examination. It frequently has happened that candidates, after having passed the reëxamination, have come to members of the Board and stated that they were very grateful for having been failed in their first examination, because they had now learned what real work and study is and have corrected their faults.

"Finally, with respect to the comments of the Board of Governors concerning the embarrassment which results from failure of men to pass the Board and thereby become eligible for Fellowship in the College: This would seem to be a question for the College to consider. The Board is not and cannot be concerned with qualifications of candidates aside from those expressed in their applications as to preparation, the opinions of physicians given as references, and their medical preparation as indicated by the written examination, by oral examination, and by their ability to handle patients and to arrive at accurate clinical diagnoses. Failure to pass the examination of the Board is no reflection on a candidate's moral or social status.

"The only object of the Board in carrying on its work is to establish and maintain standards of performance which will lead to a further improvement in scholarship

in American medicine. In carrying out this program, the Board fully recognizes its responsibility."

In answering inquiries concerning whether there has been a time limit or an age limit for certification without examination, Dr. Irons replied:

> "When the Board was first organized, it was necessary to put a time limit on applications for certification without examination. It was set at July 1, 1937, and the candidates came under certain categories: Fellowship in the American College of Physicians, membership in two of the scientific internal medical societies of national scope, and a number of others; also men recommended by the Executive Committee of the Section on Medicine of the American Medical Association. There were other men in smaller communities, often not closely associated with educational institutions, men who had never been joiners. They didn't want to join, yet they were perfectly magnificent practitioners of medicine. We included them. Since that time there have turned up a great many men who now say they would like to be certified and feel a little hurt that something hadn't been done about it, yet we couldn't do anything unless we were asked. If a man is in one of these special categories and was at least forty years of age in 1937, he can yet be certified without examination, provided all requirements are in order. If he is now over forty, it doesn't follow that he can be certified without examination, for he was only thirty-five in 1937. We are not going back of the rule, but we are just trying to correct omissions."

Motion was made to accept Dr. Irons' report, seconded and carried.

Luncheon Recess

The afternoon session was called to order by President Paullin, who asked for the report from the Committee on the Annals of Internal Medicine by Dr. Reginald Fitz, acting in the absence of Chairman Palmer. The Committee reported that at present 2,400 pages per year of scientific matter are authorized by the Board. Owing to the large number of members in the Service who had their dues remitted, thereby reducing the income, and who do not receive the Annals, and also the probability of reduction in the receipt of suitable material, the Committee considered the desirability of reducing the number of pages per year. The Editor had reported enough material on hand for at least eight months. Because the Annals has an enviable position in the field of medical literature, the Committee believes nothing should be done to jeopardize this position, but at the discretion of the Editor some reduction may be made, consistent with maintaining the journal's high standing. The Committee approved the efforts being made by the Executive Secretary to increase the income by increasing advertisements moderately and by promoting the circulation among non-members. The Committee further recommended that the Editor review the programs of "Postgraduate Nights" and Regional Meetings for material suitable for the journal; also that the Board of Regents be requested to be on the lookout for original work suitable for publication in the Annals; that the Annals be offered to the men in Service at cost ($5.00); and finally, the Committee expressed its appreciation to the Acting Editor, Dr. Paul W. Clough, for the excellent manner in which he had conducted the Annals since Editor Pincoffs entered active service.

On motion, seconded and regularly carried, the report of the Committee was accepted.

Dr. Paul W. Clough, Acting Editor, reported briefly, saying that up to that time he had received a very satisfactory number of articles and that he had 80 main articles and about 50 case histories, which had already been accepted for publication. This would be enough for eight or ten months, but at that time some marked dropping off in articles submitted is anticipated.

Dr. William B. Breed, reporting for the Board of Governors, reported as follows: "I would like to transmit an impression that I get from the Governors about these Regional Meetings. On November 9, upon return from Philadelphia after an extraordinarily successful meeting here, I wrote a letter to each Governor, pointing out the decision of that conference that we held concerning the discontinuance of the Annual Session, and asked the Governors to go into individual executive sessions to see what they may have to suggest by way of Regional Meetings in the various sections. I urgently requested that a group of Governors combine in certain sections to organize Regional Meetings. We shall hold a Regional Meeting in New England the first week in February, and cordially invite all of you to come. We expect to have Admiral McIntire, Brigadier General Grant, President Paullin, Secretary-General Piersol and other high lights of the College present. From the Governors I get the impression that while they are enthusiastic about doing something they are in doubt as to what regions should be organized. I would suggest that the Executive Secretary, Mr. Loveland, and the Committee on Postgraduate Courses and I try to decide on regions that seem appropriate and inform these Governors concerning a suggested organization; then we can say to the Governors, 'This is your region. You may not be able to have a Regional Meeting, but you belong in this setup when the time comes.' "

On inquiry from Dr. A. C. Griffith as to what part the central office plays in the conduct of Regional Meetings, the Secretary, Mr. Loveland, reported that his office prints and distributes the programs and performs every other service practically except the appointment of committees and the making up of the program itself.

Dr. O. H. Perry Pepper recommended that the Surgeon General of both the Army and Navy be invited to Regional Meetings.

Dr. Pepper, as Chairman of the Committee on Finance, reported as follows:

"1. The Committee recommends the use of the First National Bank of Philadelphia as one of the depositories of the College.

"2. The College has waived the dues of members in Service and has reduced the initiation fees to members in Service at an approximate cost for 1943 of $23,000. In conversation with the American Board of Internal Medicine, it has been suggested that that Board reduce its fee from $50.00 to $40.00 and the College reduce its initiation fee from $80.00 to $65.00. The American Board has taken this action. The Executive Secretary estimates that the proposed reduction by the College would reduce our income for 1943 by $2,850. The Finance Committee recommends that the College shall not make the proposed reduction in initiation fees, as it will apply only to members not in Service, most of whom are receiving higher professional incomes than usual because of increased work and increased ability of patients to pay.

"3. The Committee reports the following figures:

a. A year ago the surplus for 1942 was estimated at $30,000. The actual surplus has proved to be $26,515, a falling off of only $3,485.

b. The 1942 income has fallen short by an estimated $2,355.59. The 1942 expenses were $5,057.86 less than the budget.

c. The income from investments for 1942 was approximately $7,400, with trading profits of $735.83, or a total of $8,135.83.

"4. The Committee is informed that the total anticipated income of the College for 1943 will be $82,410. The Committee recommends the adoption of the proposed budgets to a total of $77,025, leaving an anticipated balance of $5,385. In addition, the Committee recommends certain small additions to the proposed budget totalling $1,215.

"5. (Thereafter the Committee's report delineated the distribution of this $1,215 among various minor accounts, including certain adjustments in salaries, etc.)

"6. The two existing research fellows will receive in 1943 a total of $2,100 if they are not called to active service. The proposed budget contains no item for additional fellowships.

"7. The proposed budget contains no items for the John Phillips Memorial Award, although a medal could be awarded at trifling cost. The main expense is usually that of travelling.

. . . . . .

"12. In the 1942 budget the sum of $2,500 was reserved for a new edition of the Directory and in the 1943 budget an additional sum of $3,000 for this purpose appears. The Committee recommends that no new edition of the Directory be published in 1943, but that these sums continue to be reserved toward the publication of a large post-war edition, containing the war record of every member.

"13. In view of the omission of the Annual Session, a stimulation of Regional Meetings seems proper, and the budget contains an item of $2,000 for this purpose. The Committee recommends an addition of $500 to this sum. The Committee also recommends that the Regents set a maximum to the amount to be contributed by the College to any one Regional Meeting. At present some of these meetings have cost the College over $500.00. The Committee recommends a maximum of $250.00.

"14. The Committee recommends the acceptance of the sales and purchases of securities suggested by Drexel & Company, its financial advisers. (Thereafter followed the specific list of securities to be purchased or sold.) The Committee recommends that any residue be invested in U. S. Savings Bonds.

"15. The College has some $27,000 in cash, of which some $3,000 is in Canada. The Committee recommends that none of this cash be invested at present.

"16. The Committee expresses its confidence and satisfaction with the management of the affairs of the College by the Executive Secretary, the Treasurer, and Drexel & Company."

Individual motions by item of the Finance Committee's report were carried, approving each recommendation. Copies of the operating statements for 1942 and the budgets for 1943 were distributed, preceding the report, to each member of the Board.

On motion by Dr. Palmer, seconded and carried, it was provided that the $5,000 previously set aside for the Directory reserve fund be diverted and appropriated for postgraduate education in military circles for 1943.

On motion by Dr. Palmer, seconded by Dr. Irons and regularly carried, it was provided that the recommendations of the Advisory Committee on Educational Policy and of the Committee on Postgraduate Courses, earlier presented in this meeting, be accepted and the program put into effect.

There followed a long discussion of the conduct of Regional Meetings, especially with regard to expenses therewith connected. It was brought out that the maximum deficit of any Regional Meeting that shall be made up by the College shall not exceed $250.00. This does not include travelling expenses of the President, because he has a separate budget, but it does include all other travelling expenses, the cost of printing the program, postage, etc. No charge is made for services performed by the Executive Offices. Social functions at Regional Meetings should be arranged so that they will carry themselves. Generally speaking, there need not be too many invited guest speakers from long distances, but rather authorities from the States represented should be placed on the program.

Dr. William D. Stroud, Treasurer, gave the following report:

"The income of the College for 1942, with estimations for the month of December, will be approximately $115,000.00; $2,300.00 less than estimated. The gross expenditures for 1942, also with estimations for December, will be approximately $82,000.00, leaving a surplus of about $26,500.00. The College operated approximately $5,000.00 below its budget.

"The book value, or purchase price, of its security holdings is:

Endowment Fund	$136,174.32
General Fund	116,521.14
	$252,695.46

"The combined present cash value (that is, Endowment Fund and General Fund) of these securities is $269,592.00.

"The College employs the same competent firm of Investment Counselors at the relatively small cost of about $400.00 per annum, and receives frequent surveys of its security holdings, which are reviewed periodically by the Finance Committee of the College.

"To December 8, 1942, we have refunded in dues a total of $7,244.00. It is estimated that the waiver of dues to Service members during 1943 will amount to approximately $15,000.00, and the reduction in Intiation Fees to Service members to approximately $8,000.00. This means a reduction in our income for 1943 of approximately $23,000.00.

"We believe the financial condition of the College sound and satisfactory. The accounts, as usual, will be audited by a certified public accountant at the end of the year, and his statements published in the 'ANNALS.'"

By motion, seconded and regularly carried, the Treasurer's report was accepted.

President Paullin introduced the subject of the election of Officers, Regents, and Governors, as well as members of the American Board of Internal Medicine during the war emergency. The Secretary reported that the Constitution and By-Laws make no provision for the election of Officers, Regents or Governors except for interim appointments in the place of those who may die or resign, except at the Annual Business Meeting of the College. He said it is not probable that an Annual Business Meeting can be held when there is no Annual Session, and the inference would be that the present Officers, Regents, and Governors should serve for the duration of the War, until the next regular election.

There followed an extended discussion. Dr. O. H. Perry Pepper expressed himself as a believer in bringing new members to the Board and resorting to any legal means possible to bring that about. President Paullin, while expressing a willingness to do whatever the Board of Regents desired, indicated his desire to be relieved as President because of a heavy burden of other duties which has fallen upon him. However, he expressed his willingness to carry on if the Board insisted.

The possibility of calling an Annual Business Meeting at the College Headquarters in Philadelphia in April was fully discussed, but the majority felt that few, if any, members of the College would attend such a meeting, and this would subject the Officers and Regents to certain criticism, for, in effect, they would be conducting the elections. The consensus in the end was that the Board had no authority to act, that the Constitution and By-Laws make no specific provisions, and since the Annual Meeting of the College has been cancelled, an act approved by the majority of members at large, the present Officers, Regents, and Governors would continue to serve until the next regular election. It was pointed out further that in most other associations

it is probable that the officers and directing bodies will be "frozen" in office in a like manner.

To fill the vacancy, July 1, caused by the resignation of Dr. J. C. Meakins as a representative of this College on the American Board of Internal Medicine, by resolution made by Dr. Griffith, seconded by Dr. Pepper and unanimously carried, Dr. James J. Waring of Denver was appointed.

President Paullin introduced a discussion with regard to arrangements for convocations for the induction of new members during the war. Secretary Loveland pointed out that two plans had been presented for consideration. First, that the College arrange regional convocations to be held at the larger Regional Meetings at which new members from those territories could be inducted. He pointed out that it is possible that no Regional Meetings will be conducted for some States. The second plan was that convocations be suspended for the period of the war, but that Fellowship certificates be issued immediately upon election and that at the end of the war a really great convocation for the induction of all these men be held. The latter plan he thought would cause a great impetus to the College and renew interest at that time.

A motion to accept the second suggestion was made by Dr. Cocke, seconded and unanimously carried.

A motion was made, seconded, and regularly carried, providing that there shall be a meeting of the Board of Regents and of the College committees at a date in April to be set by the President in consultation with the Secretary-General and the Executive Secretary. Dr. Irons announced that the American Board of Internal Medicine would meet at the same time. (The date has since been set for April 3–4, 1943.)

On motion by Dr. Fitz, seconded and regularly carried, it was resolved that the Board of Regents authorize the President to appoint a special committee, consisting of himself and the President-Elect, with the responsibility of taking the necessary steps to organize a committee on postgraduate instruction for doctors in the Armed Forces, as outlined in the resolution submitted earlier in the meeting by Dr. Bortz and adopted by the Regents.

President Paullin reported that on December 14 there would be a meeting of the War Participation Committee of the American Medical Association in Washington, at which he would present the above resolution. Thereafter he would contact the American College of Surgeons to obtain action from its executive committee. He expressed the hope that the program would be placed in action soon after the beginning of 1943, and he further gave the opinion that this is one of the most vital things that the College can do. He asked for authority to request these other organizations, if they are interested in this program, to donate funds to carry it through. On motion by Dr. Breed, seconded and regularly carried, Dr. Paullin and Dr. Irons were authorized to proceed accordingly.

ADJOURNMENT

Attest: E. R. LOVELAND, *Secretary*